Non-O Blood Type Is Associated With an Increased Risk of Venous Thromboembolism After Radical Cystectomy

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OBJECTIVE To evaluate the association of blood type (non-O vs O) with venous thromboembolism (VTE) risk after radical cystectomy (RC) for bladder cancer.

METHODS From 1980 to 2005, we identified 2076 consecutive patients with RC for whom blood type was available in 2008 (96.7%). We evaluated the association of blood type with postoperative VTE using logistic regression, controlling for patient age, tumor, and nodal stage, Eastern Cooperative Oncology Group (ECOG) performance status, body-mass index (BMI), and number of lymph nodes removed at surgery.

RESULTS A total of 865 of 2076 patients (41.7%) had O blood type, 1143 (55.0%) were non-O, and 68 (3.3%) were missing. Median follow-up was 11.1 years, during which time VTE developed in 216 patients (10.4%). No significant differences were noted between those with O vs non-O blood type regarding patient age (median 69 years vs 69, $P = .87$), ECOG ($P = .69$), BMI (median 27.5 vs 28.1, $P = .12$), tumor stage ($P = .97$), pN+ status (15.6% vs 15.2%, $P = .79$), or number of nodes removed (median 9 vs 8, $P = .43$). On multivariate analysis, non-O blood type was associated with a nearly two-fold increased risk of VTE (odds ratio [OR] = 1.85, $P = .007$).

CONCLUSION Non-O blood type was independently associated with an increased risk of VTE after RC. These patients should be counseled accordingly, and may benefit from increased perioperative prophylaxis. UROLOGY 83: 140–145, 2014. © 2014 Elsevier Inc.

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a potentially life-threatening complication after urologic cancer surgery. Radical cystectomy (RC) has been associated with the highest risk of VTE compared to any other urologic procedure, with a reported incidence ranging from 2%-10%.[1-3] The high rate of this potentially preventable complication has been the impetus for several national organizations, such as the American College of Surgeons National Quality Improvement Program, to record and use VTE events as a quality indicator in surgery. Moreover, in 2009, the American Urological Association put forth a Best Practice Statement regarding the prevention of DVT in patients undergoing urologic surgery.[4] For all patients undergoing major open urologic procedures, the American Urological Association guidelines align with the most current American College of Chest Physicians consensus statement,[5] recommending routine VTE prophylaxis in the form of low-dose unfractionated heparin, low-molecular-weight heparin, or fondaparinux 2-3 times per day, as well as graduated compression stockings and/or intermittent pneumatic compression started just before surgery and continued while the patient is not ambulating. Nevertheless, the optimal duration for prophylaxis remains to be determined. Further, the potential exists for an increased risk of bleeding complications and/or lymphocele formation with treatment.[6,7]

As such, in order to reduce VTE events and optimize patient outcomes, those persons at highest risk must be identified to allow targeted efforts at the highest risk cohort. Patients with bladder cancer undergoing RC represent a population of patients with multiple risk factors for VTE including recent surgery, immobility, active cancer diagnosis, and often as well possess the additional risk factors of advanced age, obesity, and smoking history.[8] In addition to these variables, recent hematologic research has identified blood type as a significant genetic risk factor for the development of VTE.[9-14] Specifically, among the 4 blood groups (A, B, AB, and O), patients with non-O blood type have been

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found to carry significantly increased risk for VTE, which is thought to be attributable to increased circulating levels of factor VIII (FVIII) and von Willebrand factor (VWF).[10,12,13] However, an association between blood type and VTE risk among patients with bladder cancer, who are, as noted, at a particularly high risk for these events, has, not to our knowledge, been previously established. Therefore, in this study, we sought to determine the association of blood type, collectively grouped as O-blood type and non-O blood type, with VTE risk after RC among patients with bladder cancer.

MATERIAL AND METHODS

After institutional review board approval, we reviewed the Mayo Clinic Cystectomy Registry to identify 2076 patients who underwent RC between 1980 and 2005. RC was performed by various surgeons using standard techniques. The extent of lymph node dissection varied by individual surgeon over the time period of study, but currently extends from the mid-common iliac artery proximally to Cooper's ligament distally, laterally to the genitofemoral nerve, and inferiorly to the internal iliac vessels. All specimens were re-reviewed by a single genitourinary pathologist. Tumor staging followed the 2010 American Joint Committee on Cancer/Union Internationale Contre le Cancer 7th edition TNM classification.[15] Clinicopathologic variables recorded included age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), receipt of perioperative (neoadjuvant or adjuvant) chemotherapy, pathologic tumor, and nodal stage. Neoadjuvant chemotherapy was administered within 90 days before RC and adjuvant chemotherapy up to 160 days after RC. Blood type information was cross-referenced with an institutional database maintained by the Division of Transfusion Medicine at Mayo Clinic. Blood type was available in 2008 patients (96.7%). Specific ABO genotypes were not available as patients undergoing RC typically submit a type and screen, which yields phenotypic information (A, B, AB, and O with Rh antibody) only and blood samples are not stored.

The retrospective nature of this study precluded a standardized postoperative follow-up protocol in all patients. However, follow-up after RC at our institution has generally been recommended quarterly for the first 2 years after surgery, semi-annually for the next 2 years, and annually thereafter in patients without evidence of disease recurrence. Oncologic evaluation includes history, physical examination, urine cytology, and imaging of the chest, abdomen, and pelvis. For patients followed elsewhere, the Mayo Clinic Cystectomy Registry monitors outcomes annually by correspondence to the patient and treating physician.

The primary endpoint of the study was the diagnosis of VTE after surgery. During the early half of the study period, the diagnosis of DVT was made by venography, and it was not until the late 1980s that duplex ultrasound was used to diagnose thrombus based on Doppler flow changes within the deep venous system. Similarly, the diagnosis of PE was based on arteriography or ventilation/perfusion scan interpreted by a radiologist suggestive of a high probability for PE, or if a filling defect was present on contrast-enhanced computed tomography of the pulmonary vasculature. Notably, the diagnostic evaluation of patients for VTE was based on symptom presentation and/or clinical evaluation. That is, patients did not undergo routine radiographic surveillance after surgery. Meanwhile, patients with history of VTE before RC were excluded from analysis.

Table 1. Demographics for patients with (n = 216) and without (n = 1860) venous thromboembolism

Variable	No DVT/PE (n = 1860)	DVT/PE (n = 216)	*P* Value
Age at surgery (y)			.40
Median (IQR)	68 (62-74)	69 (61-76)	
Gender			.75
Male	1498 (80.5%)	172 (79.6%)	
Female	362 (19.5%)	44 (20.4%)	
Tobacco use			.41
Missing	13 (0.7%)	0 (0%)	
No	351 (19.0%)	44 (20.4%)	
Yes (current or past)	1496 (81.0%)	172 (79.6%)	
ECOG performance status			.94
Missing	16 (0.8%)	0 (0%)	
0	1447 (78.5%)	169 (78.2%)	
1+	397 (21.5%)	47 (21.8%)	
BMI (kg/m^2)			.003
Missing	8 (0.4%)	0 (0%)	
≤25	580 (31.3%)	45 (20.8%)	
26-30	835 (45.1%)	100 (46.3%)	
31-35	332 (17.9%)	53 (24.5%)	
>35	105 (5.7%)	18 (8.3%)	
Blood type (O vs non-O)			.007
Missing	59 (3.2%)	9 (4.2%)	
O	794 (44.1%)	71 (34.3%)	
Non-O (A, B, or AB)	1007 (55.9%)	136 (65.7%)	
Rh antibody			.88
Missing	59 (3.2%)	9 (4.2%)	
Negative	297 (16.5%)	35 (16.9%)	
Positive	1504 (83.5%)	172 (83.1%)	

BMI, body mass index; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PE, pulmonary embolism.

As part of our standard perioperative management for all patients, graduated compression stockings and knee-high intermittent pneumatic compression devices were started upon entry into the operating room and continued until the patient was discharged. Early and frequent ambulation was encouraged on daily patient rounds. Unfortunately, receipt of perioperative pharmacoprophylaxis was not standardized and could not be determined for all patients in our dataset. To address this as a potential confounder, we obtained the charts of the last 100 patients in our cohort based on operative date and performed a review regarding perioperative VTE prophylaxis, which we defined as receipt of subcutaneous unfractionated heparin or low-molecular-weight heparin either preoperatively or within 1 day of surgery (surgeon preference) and was continued throughout their hospital stay.

Blood type groups were compared using Wilcoxon rank sum and chi-squared test, as appropriate. Univariate and multivariate generalized linear regression models were used to evaluate the association of various risk factors with the outcome measure of postoperative VTE. Variables found to be statistically significant on univariate analysis were selected for multivariate models. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) with *P* values ≤.05 considered statistically significant.