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Extended outpatient chemoprophylaxis reduces venous thromboembolism after radical cystectomy

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Abstract

Purpose: Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism, is a common cause of morbidity and mortality after radical cystectomy. The purpose of our study was to evaluate the utility of extended outpatient chemoprophylaxis against VTE after radical cystectomy—with a focus on any reduction in the incidence of VTE, including DVT and pulmonary embolism.

Materials and methods: Beginning in April 2013, we prospectively instituted a policy of extending inpatient VTE prophylaxis with subcutaneous heparin/enoxaparin for 30 days postoperatively. For this study, we reviewed the electronic medical records of all patients who underwent radical cystectomy at our institution from January 2012 through December 2015. The experimental group ($n = 79$) received extended outpatient chemoprophylaxis against VTE; the control group ($n = 51$) received no chemoprophylaxis after discharge. The primary outcome was the 90-day incidence of VTE. The secondary outcomes included the overall complication rate, the hemorrhagic complication rate, as well as the rate of readmission within 30 days of hospital discharge.

Results: The experimental group experienced a significantly lower rate of DVT (5.06%), assessed as of 90 days postoperatively, than the control group (17.6%): a relative risk reduction of 71.3% ($P = 0.021$). We found no significant differences in secondary outcomes between the 2 groups, including the overall complication rate (54.4% vs. 68.6%), the hemorrhagic complication rate (3.7% vs. 2.0%), and the readmission rate (21.5% vs. 29.4%).

Conclusion: Extended outpatient chemoprophylaxis significantly reduced the incidence of VTE.

Keywords: Bladder cancer; DVT; Chemoprophylaxis

1. Introduction

Radical cystectomy is the standard of care for muscle-invasive urothelial carcinoma of the bladder, but it is associated with significant morbidity (27%–57%) and mortality (0.3%–7%) [1–7]. Among cancer operations, radical cystectomy is associated with the highest readmission rate; when compared to all operations, it is second only to mitral valve replacement in terms of readmission rate [8].

Venous thromboembolism (VTE) is common after radical cystectomy (2%–24%); VTE includes both deep venous thrombosis (DVT) and pulmonary embolism (PE) [9–12]. Across all operations, postoperative VTE is associated with a nearly 4-fold increase in 30-day mortality [13]. In radical cystectomy patients, risk factors for VTE are common, including older age, male sex, chronic obstructive pulmonary disease, malignancy, chemotherapy exposure, and recent pelvic surgery [13,14]. In the postcystectomy population, the 30-day mortality from VTE increases to 6.4% [15].

Despite the adoption of inpatient postoperative chemoprophylaxis against VTE, its incidence (2%–24%) has not

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significantly changed over the last 20 years. [13] The risk of VTE likely extends beyond hospital discharge. In fact, more than 50% of the cases are diagnosed after discharge; recent studies have demonstrated that the mean time to the development of VTE is 15.2 days postoperatively [15,16].

Extended outpatient chemoprophylaxis against VTE has been well described in other fields, such as orthopedics, for high-risk patients and procedures [17]. After major abdominal or pelvic surgery, extended outpatient chemoprophylaxis against VTE with low-molecular-weight heparin (LMWH) has also been suggested [18]. For high-risk patients undergoing abdominal or pelvic surgery for cancer, the American College of Chest Physicians has recommended extended duration pharmacologic prophylaxis for VTE for 4 weeks with LMWH over limited-duration prophylaxis [19].

In our study, we evaluated the utility of extended outpatient chemoprophylaxis against VTE after radical cystectomy—with a focus on any reduction in the incidence of VTE, including DVT and PE. We defined extended outpatient chemoprophylaxis as the administration of subcutaneous LMWH or enoxaparin for 30 days following cystectomy.

2. Materials and methods

Before April 2013, standard VTE prophylaxis for cystectomy patients at our institution included preinduction prophylaxis with a single dose of subcutaneous heparin. VTE prophylaxis was continued on postoperative day 1 or 2 (based on surgeon assessment of bleeding risk) with subcutaneous heparin/LMWH throughout the remainder of the inpatient stay, stopping VTE prophylaxis on the day of hospital discharge. Beginning in April, 2013, we prospectively instituted a policy of extending inpatient VTE prophylaxis with subcutaneous heparin/LMWH for 30 days postoperatively.

For this study, we reviewed the electronic medical records of all patients who underwent radical cystectomy for urothelial carcinoma at our institution from January 2012 through December 2015. After excluding patients who were on chronic anticoagulation ($n = 7$) for other indications, as well as patients who developed DVT before discharge ($n = 20$), we analyzed the records of a total cohort of 130 patients. The experimental group ($n = 79$) received extended outpatient chemoprophylaxis against VTE; the control group ($n = 51$) received no chemoprophylaxis after discharge but did receive prophylaxis throughout their inpatient stay. Most patients in the control group underwent radical cystectomy before we instituted extended outpatient chemoprophylaxis. Several others ($n = 4$) were included in the control group because they declined home injection therapy.

The primary outcome was the incidence of VTE (including DVT and PE), assessed as of 90 days postoperatively. Diagnostic imaging studies were obtained when clinically indicated. Diagnosis of VTE was either by lower-extremity duplex ultrasound or by our computed tomography PE protocol.

The secondary outcomes included the overall complication rate, the hemorrhagic complication rate, and the readmission (within 30 d after initial hospital discharge) rate. Complications were defined as any deviation from routine postoperative care and were graded using the Clavien-Dindo classification [20]. Hemorrhagic complications were defined as any documented complaint of hematuria or bleeding as well as receiving blood transfusion within 30 days of hospital discharge. Additionally, demographic and clinical data were used to calculate the Khorana score to assess preoperative VTE risk for each patient. The Khorana score was calculated using the following 5 variables: site of cancer (2 points for very high-risk site, 1 point for high-risk site); 1 point for platelet count of 350 × 10(9)/l or more, hemoglobin less than 10 g/dl or use of erythropoiesis-stimulating agents, leukocyte count over 11 × 10(9)/l, and body mass index of 35 kg/m^2 or more. Khorana score of 0 corresponds to a low risk for DVT; a score of 1 to 2 corresponds to intermediate risk and a score of 3 or more corresponds to a high risk for DVT [21].

3. Statistical analysis

For all statistical analyses, we used the 2-tailed student t test for continuous variables and the chi-square test for categorical variables. A multivariable regression analysis was done for factors associated with DVT. Adjusted cumulative incidence rates were calculated using the Mantel-Haenzel method. We used SAS software (version 9.3) for all statistical analyses, with $P < 0.05$ considered significant.

4. Results

Demographic and clinical characteristics of the 2 groups are summarized in Table 1. The cohort consisted of 130 patients (103 men and 27 women). The extended prophylaxis group ($n = 79$) was older than the control group ($n = 51$) (mean age, 70.1 vs. 64.3 y; $P < 0.005$). The percentage of patients who received neoadjuvant chemotherapy before radical cystectomy was similar in both groups (29.4% vs. 39.2%; $P = 0.23$). Khorana score in the extended prophylaxis group was lower than the control group (1.37 vs. 1.73; $P = 0.014$). The Khorana score was not used to guide prophylaxis for VTE in either group. Surgical details are notable for shorter operative time (room in to room out) in the extended prophylaxis group (507 min vs. 561 min; $P = 0.028$). Surgical details were otherwise similar in both groups, with no significant difference in the mean number of nodes (21.4 vs. 23.0; $P = 0.48$), the percentage of robot-assisted procedures (23.1% vs 31.4%; $P = 0.28$), as well as the percentage of continent diversions (24.4% vs. 23.5%; $P = 0.95$). The mean number of days to