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Is Extended Pharmacological Venous Thromboembolism Prophylaxis Uniformly Safe Following Radical Cystectomy?

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Keywords

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Introduction

RC is the standard of care for treatment of muscle-invasive and high-risk non-muscle-invasive bladder cancer.^{1,2} RC is associated with significant perioperative morbidity and mortality.^{3–5} Deep vein thrombosis (DVT) and pulmonary thromboembolism are major and potentially lethal complications of RC. Factors such as advanced age, the presence of malignancy, pelvic lymph node dissection^{6–8}, and the use of neoadjuvant chemotherapy⁹ all cause pathologic activation of the coagulation cascade in RC patients. Since risk factors of thrombosis such as the hypercoagulable state, hemodynamic stasis, and endothelial dysfunction (Virchow's triad¹⁰) can last for many weeks,¹¹ initiation of mechanical and chemoprophylaxis prior to and immediately after the surgery has become highly encouraged by several professional organizations and is increasingly monitored as a quality of care metric.¹²

Currently, the National Comprehensive Cancer Network (NCCN)¹, United Kingdom National Institute for Health and Clinical Excellence (NICE)¹³, and Australian National Health and Medical Research Council (NHMRC)¹⁴ guidelines recommend use of extended pharmacological venous thromboembolism prophylaxis (EPVTEP) for a 4 week duration following pelvic surgery, including RC; however, experience with this strategy in RC patients is largely lacking. Importantly, low molecular weight heparin (LMWH) is renally cleared, and patients with renal deterioration risk bioaccumulation and the potential for hemorrhagic complications.^{15–17} Because RC patients often experience dehydration and secondary renal insufficiency following hospital discharge,¹⁸ we sought to quantitate the risk of clinically significant renal function decline following RC, which could result in supratherapeutic levels of LMWH and an increased risk of bleeding events.

Methods

We retrospectively reviewed our prospectively-maintained, IRB approved Fox Chase Cancer Center registry. Patients undergoing RC between 2006 and 2011 were identified. Surgical procedures were performed by six surgeons using standardized techniques for RC. Demographic data were collected including patient age, gender, race, body mass index, and utilization of any preoperative forms of anticoagulation or antiplatelet medication. Data on utilization of neoadjuvant chemotherapy, type of urinary diversion performed, estimated intraoperative blood loss, length of hospital stay, and presence of readmission within 90 days of surgery were indexed. Patient comorbidity was assessed preoperatively using American Society of Anesthesiologists (ASA) score. Pathologic information was gathered for total number of lymph nodes collected, and final pathologic stage.

Laboratory values were compiled for creatinine and estimated Glomerular Filtration Rate (GFR) at baseline and during various points within the patient's treatment course. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.¹⁹ eGFR was calculated prior to surgery, at the day of discharge, and at its lowest nadir within 90 days of discharge. Patients with eGFR <30 mL/min/1.73m² at the time of discharge were excluded from the analysis, as these individuals would not have been candidates for EPVTEP. Patients who had an eGFR greater than 30 mL/min/1.73m² following discharge were stratified in

groups based on eGFR at the time of discharge. Perioperative eGFR trends in patients who would have been candidates for extended pharmacological venous thromboembolism prophylaxis (EPVTEP) were evaluated. The postoperative surveillance and follow-up were physician- and institution-dependent, often using the recommended follow-up.¹ Length of follow-up was calculated from surgery to the date of last follow-up or death. The association between clinical characteristics and decline in renal function were assessed using multiple linear regression. Categorical predictors and outcomes were analyzed using the chi-square test. Nominal *p* values of 0.05 were used as the criterion for statistical significance. Descriptive statistics and analyses were conducted using the STATA software package (version 12; Stata Corporation, College Station, TX).

Results

Demographic information is summarized in Table 1. We identified 315 patients who underwent RC between the years of 2006 and 2011 in our registry. Eleven patients were excluded due missing data. Of the 304 patients included in the analysis, median age was 69 years (mean, 68.5; IQR, 61–76), 222 (73%) were male, and 274 (90%) were caucasian. The median preoperative ASA Score was 2 (mean, 2.2; IQR, 2–3), 80 (26%) patients underwent neoadjuvant chemotherapy and 91 (31%) patients were on either anticoagulation or antiplatelet therapy prior to surgery (aspirin 19%, warfarin sodium 6%, clopidogrel bisulfate 3%). Median intraoperative blood loss was 600 ml (mean, 794.8; IQR, 400–800), while median number of collected lymph nodes was 20 (mean, 23.1; IQR, 14–31). Continent diversion was performed in 44 (14%) of the patients. Median length of hospital stay was 8 days (mean, 12.6; IQR, 7–12).

Laboratory values for creatinine were used to calculate eGFR using the MDRD formula.¹⁹ Over forty percent (43%) of patients exhibited a decline in eGFR within the study period with the average percent reduction of 14.5% (SD 19.7%; range, 0 to –87%; IQR 0% to –25%). Of the 304 patients, 38 (13%) individuals exhibited an eGFR drop below 30 mL/min/1.73m² after discharge (Figure 1). The risks of post-discharge eGFR nadir < 30 mL/min/1.73m² was related to eGFR at discharge (Figure 2). Of 227 patients whose discharge eGFR was greater than or equal to 60 mL/min/1.73m², 12 (5%) developed a nadir eGFR of less than 30 mL/min/1.73m² during follow-up. Of the 61 patients with a eGFR between 40–60 mL/min/1.73m² at the time of discharge, 15 (25%) of experienced a nadir eGFR below 30 mL/min/1.73m². A discharge eGFR between 30–40 mL/min/1.73m² was found in 11 patients of which 6 (55%) exhibited eGFR drop below 30 mL/min/1.73m² following hospital discharge. On multivariable analysis, no association was seen between decline in eGFR and potential clinicopathologic confounders such as age (*p*=0.98), gender (*p*=0.72), race (*p*=0.98), type of diversion (*p*=0.41), length of stay (*p*=0.55), discharge Hgb (0.42), receipt of neoadjuvant chemotherapy (*p*=0.23), BMI (*p*=0.73), and ASA score (*p*=0.78).

A subanalysis of the cohort for whom eGFR was available within 30 days of discharge (*n* = 139 patients, 46% of total cohort) revealed that 12 (8.6%) individuals exhibited an eGFR drop below 30 mL/min/1.73m² after discharge. Importantly, 44 patients (32%) showed greater decline in eGFR within the initial 30 days than within 90 days of discharge.

The odds ratio for a eGFR drop below 30 mL/min/1.73m² was 1.14 (95% CI 0.84–0.91, p<0.001) for each decrease in the GFR at discharge by one mL/min/1.73m². The odds ratio for developing a GFR < 30 mL/min/1.73m² was 9.1 (95% CI 4.3–19.3, p<0.001), when comparing those with a discharge GFR ≥ 60 mL/min/1.73m² to those with a discharge GFR < 60 mL/min/1.73m².

Discussion

Some estimates place the rate of VTE events following urologic pelvic cancer surgery without appropriate prophylaxis at over 20%. Robust clinical data now support the use of thromboprophylaxis in reducing VTEs following urologic cancer surgery.²⁰ In fact, VTE prophylaxis has now become a standard quality of care metric.¹² Yet, routine use of chemical VTE prophylaxis in urologic practice is far from ubiquitous.²¹

As the urologic community works to embrace wide-spread and regular use of perioperative chemical VTE prophylaxis for inpatients, emerging data reveal that a large proportion of symptomatic VTE events after abdominal and pelvic cancer surgery occur following hospital discharge.²² Furthermore, economic pressures of today's healthcare marketplace stress faster patient transitions and shorter hospital stays.^{23–25} As such, recent guidelines by a number of leading national and international organizations have recommended EPVTEP following RC.^{1,13,14} Indeed, major abdominal and pelvic cancer surgery poses an increase in risk for post-operative DVT and fatal PE.^{5–8,20,26} The benefit of EPVTEP after major surgery, compared to those only receiving in-hospital prophylaxes, has been demonstrated by several randomized clinical trials in the surgical oncology and general surgery spaces.^{27,28} A recent meta-analysis and Cochrane database systemic review support these findings.^{28,29} Recommendations for EPVTEP following RC have largely been based on extrapolation of data gathered from patients undergoing other pelvic surgeries. Nevertheless, RC patients face a unique set of challenges following hospital discharge including pre renal, post renal and renal causes of azotemia with subsequent drops in eGFR.¹⁸ As such, the suitability of recommendations for EPVTEP in all-comers following RC requires evaluation.

The simple weight-based dosing, long half-life, subcutaneous administration and excellent bioavailability have led to wide utilization of LMWH as chemoprophylaxis against VTEs. However, a major clinical limitation of LMWHs is the necessity for adequate renal function to avoid supratherapeutic accumulation that may lead to hemorrhagic complications.¹⁵ Indeed, the highest level of accumulation in patients with impaired renal function among various LMWHs is seen with enoxaparin, the most widely utilized LMWH. Pharmacokinetic studies³⁰ have demonstrated a direct linear relationship between creatinine clearance (CrCl) and enoxaparin clearance, as measured by anti-factor Xa activity.¹⁵

A number of studies have shown an increased risk of bleeding in patients with even mildly compromised renal function. A recent meta-analysis of controlled studies confirmed higher incidence of major bleeding in patients on enoxaparin whose eGFR was ≥ 60 mL/min/1.73m².¹⁷ Although some experts recommend dose modification for patients with eGFR<30 mL/min/1.73m²,¹⁶ others advise that even with appropriate dosing changes the risk of bleeding on enoxaparin cannot be appropriately adjusted.¹⁷ DeCarolis *et al.*¹⁵ reported that 1

in every 5 patients with mildly compromised renal function (CrCl 30–50 ml/min) can develop a bleeding complication in contrast to 1 in every 20 patient with normal renal function (CrCl >60 ml/min/1.73m²). In a meta-analysis of 11,873 patients with an eGFR <60 ml/min/1.73m², the relative risk of bleeding with enoxaparin therapy was significantly increased (1.67-fold), compared with other heparins/heparinoids.¹⁷ Similarly, in our cohort, the odds ratio of post-discharge eGFR nadir of <30 ml/min/1.73m² was 9.1 in patients with discharge eGFR <60 ml/min/1.73m² compared to patients without renal compromise at hospital discharge ($p < 0.001$).

Indeed, in our cohort, a significant portion (13%) of patients who would have qualified for EPVTEP at discharge, demonstrated renal deterioration (eGFR < 30 ml/min/1.73m²) such that LMWH, had it been given as per current recommendations, may have become supratherapeutic and risked clinically significant bleeding. Patients with compromised renal function at discharge appear to represent the group at highest risk (Figure 1 and Figure 2). As such, appropriate dose modification, alternative chemical prophylaxis such as with second-generation LMWHs (eg. Bemiparin), the use of robust transition clinics, or potentially foregoing EPVTEP in these individuals might better balance risks of post-discharge VTE events against risks of clinically significant bleeding episodes.

Although our study is the first to bring forward a potential patient safety concern with regard to use of EPVTEP in all-comers who undergo RC, the data need to be interpreted in the context of their limitations. In addition to shortcomings inherent to all single-institution retrospective analyses, patients in this cohort did not receive EPVTEP. As such, actual bleeding risks cannot be quantitated, since not all patients with eGFR < 30 ml/min/1.73m² will experience bleeding. Furthermore, it is not possible to examine whether other patient risk-factors such as comorbidities, performance status, or use of neoadjuvant chemotherapy would contribute to risks of bleeding during EPVTEP. Importantly, the core analysis of this manuscript was performed on data within 90 days of discharge, while EPVTEP is generally recommended for only 30 days. Nevertheless, when analysis was limited to patients for whom 30 day data points were available, results remained unchanged. As such, we believe that the data presented raise legitimate clinical quality of care concerns regarding the use of EPVTEP in patients who exhibit renal insufficiency at the time of hospital discharge following RC.

Conclusions

A large portion of patients undergoing RC experience a decline in eGFR following discharge. While post-operative VTE following RC is a recognized concern, a better understanding of risks of EPVTEP is needed before routine post discharge use is universally adopted in patients undergoing RC. Our data suggest that patients with eGFR >60 mL/min/1.73 m² are best suited for EPVTEP, while safety of the EPVTEP clinical strategy in patients with even mildly compromised renal function at discharge requires further investigation and affords opportunities for optimization in transition of care processes.

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Figure 1.
Summary of Chronic Kidney Disease (CKD) stages in RC patients before surgery and after discharge.

Figure 2. Relationship between eGFR at the time of discharge and the probability of post-discharge nadir eGFR < 30 ml/min/1.73m².

Table 1

Patient demographics

Characteristics	Number (IQR or %)
Age (y)	69 (61–76)
Sex (male)	222 (73)
Race (white)	274 (90)
Body mass index (kg/m ²)	26.9 (24.2–31.3)
ASA score	2 (2–3)
Preoperative ASA, Plavix, Coumadin, LMWHs	91 (31)
Continent urinary diversion	44 (15)
Estimated blood loss (mL)	600 (400–800)
Number of nodes	20 (14–31)
Length of stay (d)	8 (7–12)
Neoadjuvant chemotherapy	94 (31)
90-D readmission	87 (29)
Length of follow-up (mo)	29.8 (5.9–46.1)
Pathologic T stage	
pTo	39 (13)
pTis	33 (11)
pTa	11 (4)
pT1	14 (5)
pT2a	21 (7)
pT2b	31 (10)
pT3a	61 (20)
pT3b	33 (11)
pT4a	49 (15)
pT4b	12 (4)
Pathologic N stage	
pN0	225 (74)
pN1	27 (9)
pN2	42 (14)
pN3	10 (3)

ASA, American Society of Anesthesiologist; IQR, interquartile range; LMWHs, low-molecular-weight heparins.