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# Prophylactic enoxaparin doses may be inadequate in patients undergoing abdominal cancer surgery

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ABSTRACT

*Background:* The incidence of venous thromboembolism has increased in patients following cancer surgery despite the increased use of prophylactic anticoagulants, suggesting standard doses may be inadequate. We sought to determine the adequacy of enoxaparin prophylaxis in patients undergoing abdominal cancer surgery.

*Methods:* Peak and trough anti-Xa levels were measured in patients receiving enoxaparin thromboprophylaxis (40 mg daily or 30 mg twice daily, at the surgeon's discretion) after undergoing open abdominal cancer surgery at a single institution.

*Results:* Fifty-five patients received enoxaparin 40 mg daily (group 1), 18 received 30 mg twice daily (group 2; total $n = 73$). There were no significant differences in gender, age, body mass index, creatinine clearance, diagnosis, or procedure between the two groups. Thirty-nine patients (53.4%) had inadequate peak anti-Xa levels (<0.2 IU/mL) and 69 patients (94.5%) had inadequate trough levels (≤0.1 IU/mL). Group 2 had lower mean peak levels (0.14 ± 0.02 IU/mL) than group 1 (0.22 ± 0.01, $P = 0.003$), and higher mean trough levels (0.06 ± 0.017) than group 1 (0.02 ± 0.004, $P = 0.033$). Group 2 had lower incidence of adequate peak anti-Xa levels than group 1 when adjusting for gender, age, body mass index, and preoperative creatinine clearance (OR 0.23, $P = 0.039$).

*Conclusions:* The majority of patients had inadequate anti-Xa levels following abdominal cancer surgery, calling into question standard prophylactic enoxaparin dosing.



## Introduction

Following surgery, cancer patients are at high risk of venous thromboembolism (VTE) due to the presence of two major risk factors—malignancy and major surgery.[1] Cancer increases the risk of VTE through several mechanisms including mucin production by tumors, tissue-factor exposure, cysteine protease-mediated thrombin induction, local hypoxia,

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mechanical stasis, and other factors.[2,3] Surgery increases the risk of VTE by contributing to vascular injury, immobility, and venous stasis. Despite modern techniques of postoperative VTE prophylaxis, deep venous thrombosis (DVT) and pulmonary emboli (PE) occur in 1%-7% of the patients undergoing major cancer surgery,[4-6] with a 12% mortality[5] and a cost of $1.5 billion in the United States annually.[7] Given the morbidity, mortality, and cost associated with VTE, patients undergoing major cancer surgery are recommended to receive postoperative pharmacologic thromboprophylaxis by multiple major guidelines.[8,9]

Low molecular weight heparin (LMWH) has advantages over unfractionated heparin as a pharmacologic VTE prophylaxis agent in terms of prolonged half-life and predictable bioavailability. Enoxaparin is a widely used LMWH for postoperative VTE prophylaxis and is safe and effective in cancer surgery patients.[10] Enoxaparin acts primarily through antithrombin III and its downstream clotting factors, in addition to inhibiting factor Xa. Standard coagulation parameters (prothrombin time or partial thromboplastin time) are not altered by enoxaparin, but plasma anti-Factor Xa (anti-Xa) levels can be monitored as a marker of enoxaparin efficacy.[11] Peak and trough anti-Xa levels can be measured, and adequate peak and trough levels for VTE prophylaxis have been proposed.[12,13]

Enoxaparin is FDA approved for VTE prophylaxis in two doses—40 mg daily for abdominal surgery or 30 mg twice daily for hip or knee replacement, although both doses are frequently used after major abdominal cancer surgery. Enoxaparin dosing is not weight or drug-level based, due to its predictable pharmacokinetic and pharmacodynamic profile, except in those with morbid obesity or renal insufficiency.[14,15] However, some have questioned this approach as the VTE rate in cancer surgery patients has risen despite the increased utilization of pharmacologic prophylaxis.[5] Several studies have found critically ill, trauma and burn, and plastic surgery patients often have low plasma anti-Xa levels, which is associated with an increased incidence of DVT.[16-20]

We sought to measure peak and trough anti-Xa levels and perform DVT ultrasound screenings in patients undergoing major open abdominal surgery for cancer at our institution, to determine the adequacy of pharmacologic VTE prophylaxis. We hypothesized that a large number of patients in this population will have inadequate anti-Xa levels with standard enoxaparin dosing.

## Methods

### *Design and eligibility*

This was an IRB-approved, prospective, single-arm, single-institution, observational study. Patients undergoing major, open abdominal surgery for cancer were screened for study eligibility and consented to enter the study. Patients who had no contraindication to postoperative enoxaparin VTE prophylaxis were included. Patients with a history of prior VTE or who were on therapeutic anticoagulation were excluded.

### *Thromboprophylaxis*

Participants received one of two standard prophylactic enoxaparin doses (40 mg daily or 30 mg twice daily) at the discretion of the treating clinician. Preoperative subcutaneous heparin and the postoperative enoxaparin timing and duration were also at the discretion of the treating clinician, but enoxaparin was typically given on the first postoperative day, continued throughout the entire hospital stay, and for two additional weeks after discharge. All patients received mechanical DVT prophylaxis and early ambulation protocols, which included being out of bed to chair on postoperative day one, and ambulating on postoperative day two and thereafter (unless physically unable to do so).

### *Anti-Xa measurements and data collection*

Anti-Xa assays were analyzed on ACL TOP machines (Beckman Coulter, Brea, CA) using the HemosIL heparin anti-Xa chromogenic assay. Peak serum anti-Xa levels were drawn 3–5 hours after at least the third consecutive dose and trough serum anti-Xa levels were drawn within 1 hour prior to the fourth consecutive dose. Patients who missed LMWH doses had peak and trough levels drawn after at least the third and prior to at least the fourth consecutive dose, respectively, without intervening missed doses. Those patients who switched doses were assigned to a dose group corresponding to the dose from which their anti-Xa levels were drawn. Peak anti-Xa levels of $\geq$0.2 IU/mL and trough anti-Xa levels of >0.1 IU/mL were considered adequate for VTE prophylaxis.[12,13] No enoxaparin dose adjustments were made based on anti-Xa levels in this study. Bilateral lower extremity duplex ultrasound (US) examinations were performed postoperatively (within 72 hours after surgery) and before discharge from the hospital (within 72 hours before discharge). Patients were given at least 2 weeks of postdischarge enoxaparin, per standard practice at UCSD for surgical oncology patients. Duplex US screening was not performed after discharge unless clinically indicated. Additional participant data collected included age, gender, body mass index (BMI), diagnosis, procedure, preoperative creatinine clearance (CrCl), peak postoperative creatinine, and 30-day clinical VTE diagnosis.

### *Statistics*

Baseline characteristics were compared between each dosing group. Normality was assessed visually by box plots and Q-Q plots, and quantitatively by Kolmogorov–Smirnov and Shapiro–Wilk tests. A Student t test was used to compare the means of continuous normally distributed variables, Kruskall–Wallis test was used to compare continuous non-normally distributed variables, and a Fisher's exact test was used to compare proportions of categorical/binary variables. Levene's test was conducted to determine whether equal variances could be assumed. Univariate and multivariate regression models were used to analyze the association of gender, age, BMI, preoperative CrCl, and dose with the proportion of adequate peak anti-Xa levels; as these factors were associated with anti-Xa levels in other studies.[14,15,18,21,22] A sample size of approximately 75 patients was estimated to