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Identifying risk factor for development of perioperative venous thromboembolism in patients with gastrointestinal malignancy

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ABSTRACT

Background: Current data suggests that decreasing VTE incidence may require focus on other factors. This study aimed to identify perioperative risk factors for VTE in patients undergoing surgery for gastrointestinal (GI) malignancy.

Methods: Patients undergoing surgery for GI malignancy from 2013 to 2016 were grouped according to whether or not they developed a postoperative VTE, and groups were compared along demographic, perioperative, and outcome variables.

Results: Patients who developed VTE were more likely to be older (67 ± 11 VTE vs. 61 ± 10 no VTE, $p = 0.04$), male (92% vs. 59%, $p = 0.02$), and have a history of atrial fibrillation (39% vs. 11%, $p = 0.01$). They also experienced higher intraoperative blood loss (328 ± 724 mL no VTE vs. 918 ± 1885 mL VTE, $p = 0.01$). On multivariable analysis, history of atrial fibrillation was independently associated with development of postoperative VTE (odds ratio = 3.83, 95% confidence interval = 1.13–13.05, $p = 0.03$).

Conclusion: A prior history of atrial fibrillation independently predicts increased risk of developing VTE after surgery for GI malignancy. Improving understanding of the underlying VTE pathophysiology in these patients can help guide effective prevention strategies.

Introduction

Venous thromboembolism (VTE) represents clinically significant problem among surgical patients, particularly those with malignancy.[1–4] Over the past 20 years, VTE has garnered increasing attention in the surgical oncology community, and significant efforts have been undertaken to decrease incidence of clinically significant VTE among patients.[3,5,6] Indeed, quality metrics and postoperative care pathways routinely include mechanical and chemoprophylaxis as well as early ambulation after surgery to help minimize the number of patients who develop VTE after surgery.[7]

While the aforementioned efforts to decrease incidence of clinically significant VTE among surgical oncology patients have helped improve rates of postoperative VTE, rates still remain around 3–5%.[8] Moreover, accurately predicting patients who will develop VTEs remains challenging despite the development of scoring systems and predictive models.[9,10] This holds particularly true among patients undergoing surgery for gastrointestinal (GI) malignancy given the coexistence of several risk factors for VTE.[1,4,11]

Taken together, current data suggests that further decreasing VTE incidence may require focus on other perioperative factors to identify patients most likely to benefit from more aggressive prophylaxis strategies and more intense perioperative screening for VTE. This study aimed to identify perioperative risk factors for clinically significant VTE in patients undergoing surgery for gastrointestinal (GI) malignancy.

Methods

Patient selection

A University of Louisville Institutional Review Board-approved single-institution database was queried for patients undergoing surgical intervention for gastrointestinal malignancy from 2013 to

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2016. Patients were grouped according to whether or not they developed a clinically significant VTE (deep venous thrombosis (DVT) and/or pulmonary embolus (PE)) during the perioperative period (specifically, during the index hospitalization). Clinically significant VTE was defined as any DVT or PE that resulted in signs and or symptoms prompting diagnostic evaluation (with lower extremity duplex and/or CT angiography of the chest), was confirmed by diagnostic imaging, and required subsequent therapeutic intervention.

Data collection and cohort comparison

Groups were compared with respect to demographic variables, including age, gender, body mass index (BMI), history of tobacco use, history of atrial fibrillation, and history of VTE, as well as the type of malignancy treated and the receipt of preoperative chemotherapy and/or radiation. Patients were also compared along intraoperative (type of procedure performed (gastroesophageal (GE) versus hepatopancreatobiliary (HPB)), operating room time, estimated blood loss, intraoperative fluid administration) as well as perioperative (whether they were treated using an enhanced recovery after surgery (ERAS) pathway, use of an epidural for pain control, requirement for intensive care unit admission/mechanical ventilation/blood transfusion postoperatively) details. Receipt of VTE chemoprophylaxis in accordance with our institutional protocol (subcutaneous heparin 5000 units every 8 h, subcutaneous enoxaparin 40 mg daily, or alternative chemoprophylaxis agent) was also compared. Finally, groups were compared with respect to incidence and nature of non-VTE complications as well as overall length of stay (LOS).

Statistical analysis

Categorical variables were compared using Fisher's exact test or chi-square test as appropriate. Continuous variables were compared using two-sided student's t-test. Multivariable analysis was performed using logistic regression. All statistical analyses were performed using Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, La Jolla, California, USA) and MedCalc version 17.9.7 (MedCalc Software, Ostend, Belgium). For all analyses, $p < 0.05$ was considered significant.

Results

Of 363 total patients, 13 (3.6%) developed perioperative VTE. Of these, one (7.7%) had a pulmonary embolus (PE) alone, eight (61.5%) developed a deep venous thrombosis (DVT) alone, and four (30.8%) had both a DVT and a PE. Patients who developed VTE were more likely to be older (67 ± 11 years VTE vs. 61 ± 10 years no VTE, $p = 0.04$), male (92% VTE vs. 58% no VTE, $p = 0.03$), and have a history of atrial fibrillation (33% VTE vs. 11% no VTE, $p = 0.04$) (Table 1). One of the five of the patients with atrial fibrillation was on chronic anticoagulation at the time of their operation. This was held five days prior to surgery. Decisions regarding pharmacologic anticoagulation were made by the patient and they primary care doctor or cardiologist based on bleeding risk, risk of thromboembolic events, and other pertinent factors. Of note, all patients had appropriate rate and/or rhythm control with appropriate medications. Patients did not differ with respect to BMI, history of tobacco use, history of VTE, type of malignancy, or preoperative therapy.

Intraoperatively, while patients who developed VTE did not differ from those that did not develop VTE with respect to total operating room time (174 ± 98 min VTE vs. 167 ± 107 min no VTE, $p = 0.55$), they did experience higher estimated blood loss (328 ± 724 mL vs. 918 ± 1885 mL, $p = 0.01$) (Table 2). Patients did not differ with respect to type of surgery (HPB vs. GE) intraoperative crystalloid administration. Postoperatively, patients differed only with respect to type of chemoprophylaxis received, with patients who developed VTE being less likely to receive enoxaparin than their no VTE counterparts (76.9% VTE vs. 90.6% no VTE, $p = 0.03$) (Table 3). Additionally, patients who developed VTE trended toward having a greater requirement for blood transfusion (38.5% VTE vs. 17.1% no VTE, $p = 0.06$) and mechanical ventilation (23.1% VTE vs. 6.6% no VTE, $p = 0.06$), though these trends did not reach statistical significance. Groups did not differ with respect to treatment along an enhanced recovery pathway or ICU admission.

Regarding perioperative outcomes, patients who developed VTE did not differ from their no VTE counterparts in terms of postoperative complication rate or grade (Table 3). They were more likely to develop postoperative renal failure (15.4% VTE vs. 2.3% no VTE, $p = 0.045$), but there were no other differences with respect to complication type. Additionally, there was no difference with respect to length of stay.

On multivariable analysis controlling for age, gender, history of atrial fibrillation, and receipt of enoxaparin, a history of atrial fibrillation was independently associated with development of postoperative VTE (odds ratio = 3.83, 95% confidence interval = 1.13–13.05, $p = 0.03$). No other variables were independently associated with development of VTE.

Table 1
Demographic, tumor, and treatment characteristics.

	No VTE (n = 350)	VTE (n = 13)	p-value
Age (years)	61 ± 10	67 ± 11	**0.04**
Male Gender	208 (59.4%)	12 (92.3%)	**0.02**
Body mass index (BMI)	28 ± 6	27 ± 4	0.55
History of Atrial Fibrillation	39 (11.1%)	5 (38.5%)	**0.01**
History of VTE	10 (2.9%)	1 (7.7%)	0.33
Tobacco Use	111 (31.7%)	4 (30.8%)	1.00
Prior thoracic/abdominal surgery	282 (80.6%)	12 (92.3%)	0.48
Malignancy type			
Esophageal	74 (21.1%)	2 (15.4%)	0.49
Gastric	35 (10.0%)	1 (7.7%)	
Pancreatic/Periampullary	90 (25.7%)	2 (15.4%)	
Biliary	19 (5.4%)	0 (0.0%)	
Hepatocellular	30 (8.6%)	2 (15.4%)	
Hepatic metastases	83 (23.7%)	6 (46.2%)	
Other	19 (5.4%)	0 (0.0%)	
Preoperative therapy	161 (46.0%)	8 (61.5%)	0.40
Chemotherapy only	96 (27.4%)	5 (38.5%)	0.36
Chemotherapy + radiation	65 (18.6%)	3 (23.1%)	0.72
Operation Type			
HPB	241 (68.9%)	10 (76.9%)	0.76
GE	109 (31.1%)	3 (23.1%)	

*Categorical variables expressed as n (%). Continuous variables expressed as mean ± standard deviation.

Discussion

This study demonstrates that a history of atrial fibrillation independently predicts patients undergoing surgery for GI malignancy at higher likelihood of developing clinically significant perioperative VTE. These findings can help guide both prophylaxis and screening strategies in these patients to mitigate their risk of VTE development.

As previously mentioned, several groups have worked to identify risk factors for development of perioperative VTE among patients with malignancy and incorporate those into scoring systems for use in risk stratification.[2,8,11] These studies demonstrated a number of factors for VTE in both oncology patients, including malignancy type (particularly gastric, pancreatic, and lung), older age (i.e. > 60–65), multiple comorbidities, obesity, receipt of

Table 2
Perioperative details.

	No VTE (n = 350)	VTE (n = 13)	p-value
Enhanced recovery (ERAS) pathway	144 (41.1%)	4 (30.8%)	0.57
Operating room time (minutes)	167 ± 107	174 ± 98	0.82
Intraoperative crystalloid administered (mL)	1422 ± 811	1461 ± 934	0.87
Estimated blood loss (mL)	328 ± 724	918 ± 1885	**0.01**
Epidural catheter	144 (41.1%)	4 (30.8%)	0.57
VTE chemoprophylaxis	299 (85.4%)	13 (100.0%)	0.23
Heparin	26 (8.7%)	2 (15.4%)	**0.03**
Low molecular weight heparin (Lovenox)	271 (90.6%)	10 (76.9%)	
Other	2 (0.7%)	1 (7.7%)	

*Categorical variables expressed as n (%). Continuous variables expressed as mean ± standard deviation.

antineoplastic agents, and, in surgical oncology patients, extended operating room time (i.e. > 2 h) and bed rest (i.e. > 3 days).[2,8,11] Interestingly, in the present study focusing solely on patients undergoing surgery for GI malignancy in the era of aggressive early ambulation, routine use of postoperative chemoprophylaxis, and increasing use of preoperative chemotherapy with or without radiation, none of these were independently associated with VTE postoperatively. While this could be the result of a relatively small number of patients who developed DVT, focus on the perioperative period rather than a more prolonged postoperative window (i.e. 30 or 90 days postoperatively), it suggests that efforts at further decreasing perioperative VTE rates should at least consider changing risk stratification methods for surgical oncology patient with GI malignancy and perioperative management of these patients.

The association of atrial fibrillation with perioperative VTE demonstrated in the present study represents a logical extension of the existing medical literature regarding thromboembolism in non-surgical patients with atrial fibrillation.[12–14] Combining this known risk factor for VTE with those of malignancy and surgery likely has at least an additive, if not a synergistic effect, on hypercoagulability in patients GI malignancy. Thus, even incorporating risk factors for VTE in these patients (e.g. older age, male gender) may not sufficiently approximate VTE risk in patients who are also undergoing surgery for malignancy.[15–17] In these patients, the major issue that arises is interruption of preoperative systemic anticoagulation to minimize bleeding risk during major surgery. In general, decreasing risk of VTE would involve incorporation of a bridging therapy (i.e. continuous heparin infusion or 1 mg/kg ideal body weight enoxaparin daily) during the time when the patient is unable to take their long-term anticoagulation or the levels thereof are subtherapeutic.[18]

Table 3
Postoperative outcomes.

	No VTE (n = 350)	VTE (n = 13)	p-value
ICU stay	106 (30.3%)	7 (53.8%)	0.12
ICU LOS (days)	5.7 ± 6.8	5.3 ± 3.1	0.40
Ventilator requirement	23 (6.6%)	3 (23.1%)	0.06
Ventilator days	5.8 ± 6.7	2.7 ± 1.2	0.44
Blood transfusion requirement	60 (17.1%)	5 (38.5%)	0.06
Complication (other than VTE)	149 (42.6%)	6 (46.2%)	0.78
Abscess	8 (2.3%)	0 (0.0%)	1.00
Anastomotic leak	7 (2.0%)	0 (0.0%)	1.00
Bile leak	2 (0.6%)	0 (0.0%)	1.00
Bowel obstruction/ileus	26 (7.4%)	2 (15.4%)	0.26
Cardiac dysrhythmia	11 (3.1%)	1 (7.7%)	0.36
Feeding tube malfunction	7 (2.0%)	0 (0.0%)	1.00
Hepatic dysfunction	6 (1.7%)	0 (0.0%)	1.00
Pleural effusion	20 (5.7%)	0 (0.0%)	1.00
Pneumonia	14 (4.0%)	2 (15.4%)	0.11
Renal failure	8 (2.3%)	2 (15.4%)	**0.045**
Urinary tract infection	6 (1.7%)	0 (0.0%)	1.00
Wound infection	12 (3.4%)	1 (7.7%)	0.38
Other infection	22 (6.3%)	0 (0.0%)	1.00
Complication grade	2.2 ± 1.1	2.0 ± 1.5	0.67
Length of stay (days)	8.4 ± 7.7	9.1 ± 5.3	0.75

*Categorical variables expressed as n (%). Continuous variables expressed as mean ± standard deviation.

For both patients with prior history of atrial fibrillation and other high-risk patients identified in previous analyses, the question of how to optimally prophylax against VTE in these patients remains. More aggressive chemoprophylaxis, such as higher dosing of enoxaparin (i.e. ≥40 mg subcutaneously every 12 h) or the aforementioned appropriate bridging therapy, may more effectively prevent VTE but may also result in a higher incidence of clinically significant postoperative bleeding. Alternatives could include preoperative chemoprophylaxis in addition to inferior vena cava (IVC) filter placement. With respect to the former, previous work has demonstrated safety and efficacy of preoperative chemoprophylaxis strategies (40 mg subcutaneous enoxaparin or 5000 units subcutaneous unfractionated heparin within 2 h of surgery) in patients with a variety of malignancies.[19] Not only did these patients have lower documented rates of VTE, but they also had lower rates of bleeding and were less likely to require blood transfusion than their counterparts treated prior to implementation of the preoperative chemoprophylaxis protocol. With regards to the latter, retrospective studies have demonstrated a decreased rate of PE in select high risk patients.[20–22] However, no prospective data exists with respect to the benefits of employing such a strategy outside of high risk patients with a contraindication to chemoprophylaxis or those with a history of recurrent VTE despite receiving appropriate medical therapy. Still, prophylactic retrievable IVC filters in the perioperative setting may indeed provide additional protection in appropriately selected patients.[20,21]

An additional question in these high risk patients remains whether or not these patients had clinically silent VTE prior to surgery. In such cases, surgical stress could have resulted in VTE propagation and transformation into a clinically significant entity. Several groups have assessed the utility of preoperative VTE screening in surgical patients using plasma D-dimer followed by duplex ultrasound of the lower extremities and chest CT angiogram in patients with abnormally elevated results.[23,24] Such practices in surgical oncology patients with upper GI malignancy could help optimally select patients in need of preoperative intervention, including possible IVC filter, preoperative VTE prophylaxis, and more aggressive postoperative prophylaxis.

This study should be interpreted in light of several limitations. The single-center, retrospective nature of the analysis limits the strength of this study's conclusions. Additionally, the small number of patients who developed postoperative VTE limits the power of this study, and the lack of a validation dataset in which to assess the findings reported herein prevents us from making any claims about the generalizability of said findings. Finally, data regarding patient compliance with medications for their atrial fibrillation in the

preoperative period could not be readily obtained from patient charts.

Conclusions

A prior history of atrial fibrillation independently predicts patients at increased risk of developing clinically significant VTE after surgery for GI malignancy. Future studies focused on improving understanding of the underlying pathophysiology of VTE in these high-risk patients can help guide development of effective prevention strategies.

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