2009

Retrospective Evaluation of Venous Thromboembolism Prophylaxis in the Adult Cancer Population

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J Oncol Pharm Practice (2009) 00: 1–5

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Study objectives. Hospitalized cancer patients are at an increased risk for venous thromboembolism (VTE) and it is recommended they receive pharmacologic prophylaxis unless otherwise contraindicated. The majority of data supporting this recommendation comes from sub-group analyses and extrapolation of data gathered in general medical/surgical patients. This study seeks to assess the safety and efficacy of VTE prophylaxis in cancer patients admitted to our institution.

Methods. Charts of patients 18–89 years of age receiving VTE prophylaxis with unfractionated heparin, low molecular weigh heparin, or fondaparinux while admitted to Karmanos Cancer Center between September and October 2007 were retrospectively reviewed. Risk factors for VTE were assessed and the efficacy/safety of the prophylactic agents was compared.

Results. One-hundred and eighty consecutive patients were identified. The average number of risk factors for developing VTE was 3–4 per hospital admission in addition to an active cancer diagnosis. Three VTEs occurred in the heparin group with two patients experiencing a VTE during their admission and one experiencing a VTE within 1 month after discharge. Four (2.6%) patients receiving heparin had a major bleeding event. Minor bleeding occurred in 14.3, 11.5, and 22.2% of patients receiving heparin, enoxaparin, and fondaparinux, respectively.

Conclusions. This retrospective study showed cancer patients are at increased risk for VTE, typically with 3–4 risk factors per admission. VTEs were uncommon; however, three patients receiving heparin experienced a VTE and four had a major bleeding event. Minor bleeding rates were similar among groups. ***J Oncol Pharm Practice (2009) 00: 1–5.***

Key words: venous thromboembolism; heparin; enoxaparin; fondaparinux; prophylaxis

BACKGROUND

Patients diagnosed with cancer are at an increased risk for venous thromboembolism (VTE) and recurrent VTE has also been more frequently observed.[1,2] In the hospitalized general medical/surgical population, the prevalence of VTE ranges from 10% to 40%.[1] Cancer alone is associated with a 4-fold greater VTE risk compared to this general population, especially among those receiving active therapy for their malignancy.[2] Additionally, cancer patients undergoing surgery have twice the risk for post-operative deep venous thrombosis (DVT) and three times the risk for pulmonary embolism (PE).[1]

Currently the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), and the National Cancer Care Network (NCCN) provide guidelines for the management and prevention of VTE in cancer patients.[1–3] Though there are some differences in the identified risk factors for VTE among these consensus guidelines,

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10.1177/1078155209104379

common risks agreed upon by all three include active cancer, increased age, obesity, history of prior VTE, heritable prothrombotic mutations, surgery, hospitalization/acute medical illness, chemotherapy, erythropoietic stimulating agents, and hormonal therapy.

Pharmacologic prophylaxis has been shown to decrease the rate of VTE in various settings.[1–3] Available prophylactic anticoagulants include unfractionated heparin (UFH), low molecular weight heparins (LMWH), and fondaparinux. All three available guidelines currently recommend pharmacologic VTE prophylaxis with one of the aforementioned agents in cancer patients admitted to the hospital without contraindications.[1–3] This recommendation is largely based on evidence and experience from the general medical and surgical patients, as there is limited data specifically evaluating the impact of such prophylactic measures in cancer patients. The purpose of this study was to retrospectively assess and compare the efficacy and safety of VTE prophylaxis practices in the cancer population admitted to our institution.

METHODS

Study population

Cancer patients admitted to our institution from September to October 2007 receiving prophylactic anticoagulants were identified by searching the pharmacy's electronic database. Patients were excluded if they received prophylaxis for less than 1 day, if they were pregnant, were younger than 18 or older than 89 years of age. Pharmacologic prophylactic agents utilized included UFH, enoxaparin, and fondaparinux.

Data collection

Patients included in this study had both their electronic and paper-based medical record reviewed for the duration of their hospital stay and for 4 weeks after discharge. Data collection included demographic data, risk factors for VTE development, symptomatic VTE, major and minor bleeding, and laboratory results (hemoglobin, platelets, serum creatinine).

Endpoints

The primary endpoint was to compare both the symptomatic VTE rate during hospitalization and within 4 weeks of hospital discharge between the three prophylactic agents. VTE was defined as either DVT or PE. Secondary endpoints included the safety outcomes of the anticoagulants utilized during hospitalization and an assessment of the risk factors patients possessed. Major bleeding was defined as intracranial or retroperitoneal bleeding, bleeding resulting in >2 g/dL drop in hemoglobin, or that leading to transfusion or death. Minor bleeding was also assessed and included all bleeding besides that meeting criteria for major bleeding. Heparin-induced thrombocytopenia (HIT) was defined according to the following: a platelet drop to $<100{,}000/mm^3$ or >50% decline, inflammation and/or necrosis at the heparin injection site, positive platelet factor 4 dependant immunoassay with clinical signs of HIT, or development of new arterial or venous thrombotic event with clinical signs of HIT.

ACCP, ASCO, and NCCN guidelines were utilized in choosing risk factors to evaluate. Those appearing in $\geq$2 of the guidelines were chosen, and include: active cancer, age >65, body mass index (BMI) $>30\,kg/m^2$, prior VTE, heritable prothrombotic mutations, surgery, hospitalization/acute medical illness, infection, lung disease, congestive heart failure, and receipt of chemotherapy or hormonal therapy.

Statistical analysis

Chi-squared and analysis of variance (ANOVA) was utilized to compare continuous variables. Ordinal data was compared with Kruskal–Wallis one-way analysis of variance. Statistical significance was defined as a p-value <0.05. SPSS v10.0 (SPSS Incorporated, Chicago, IL) statistical software was used to analyze the data.

This study was approved by the Human Investigation Committee at Wayne State University and the Protocol Review and Monitoring Committee at Karmanos Cancer Center.

RESULTS

Patients

One-hundred and eighty patients were identified and included in the study. Heparin was the anticoagulant used for 144 (80%), enoxaparin for 23 (13%), fondaparinux for 9 (5%), and multiple agents for 4 (2%) patients. These patients accounted for 193 admissions within the 2-month period of time that data collection occurred (154 (80%) heparin; 26 (13%) enoxaparin; 9 (5%) fondaparinux; 4(2%) multiple agents during hospital stay). The four patients who had prophylactic drugs changed during their admission were excluded from this analysis. Overall, baseline characteristics were similar between groups (Table 1).

Table 1. Baseline characteristics

	Heparin $n=144$	Enoxaparin $n=23$	Fondaparinux $n=9$
		Mean ± SD	
Age (years)	57.7 ± 13.7	60.1 ± 9.2	57.4 ± 11.2
Body mass index (kg/m^2) [a]	25.9 ± 6.6	31.7 ± 10.7	26.4 ± 11.2
Length of stay (days)	7.5 ± 6.3	8.3 ± 5.7	11.2 ± 7.2
Length of prophylaxis (days)	5.9 ± 4.28	6.5 ± 4.34	7.7 ± 6.38
		No. of patients (%)	
Male	71 (49.3)	5 (21.7)	4 (44.4)
Race			
White	71 (49.3)	12 (52.2)	5 (55.6)
Black	64 (44.4)	9 (39.1)	3 (33.3)
Hispanic	1 (0.7)		1 (11.1)
Asian	2 (1.4)		
Other	1 (0.7)		
Unknown	5 (3.5)	2 (8.7)	
Diagnosis			
Myeloma	3 (2.1)		
Lymphoma	10 (6.9)		
Leukemia	4 (2.8)		1 (11.1)
Gastrointestinal	31 (21.5)	4 (17.4)	1 (11.1)
Breast	15 (10.4)		
Thoracic/Head & neck	44 (30.6)	2 (8.7)	6 (66.7)
Gynecological	8 (5.6)	17 (73.9)	
Genitourinary	11 (7.6)		
Other	18 (12.5)		1 (11.1)

[a]*Bonferroni Correction: difference between heparin and enoxaparin groups (p = 0.002).*

There was a statistical difference in body mass index ($p = 0.003$), which was determined to be between the heparin and enoxaparin groups after Bonferroni correction ($p = 0.002$).

The majority of patients on heparin (80%) received 5000 units subcutaneously every 8 h, and 84.6% of those on enoxaparin received 40 mg daily. All patients in the fondaparinux group received 2.5 mg daily.

Risk factors for VTE

On an average, patients in the study had 3–4 risk factors per hospital admission in addition to their active cancer diagnosis. The most common risk factors among the three prophylactic anticoagulant groups included obesity (22.2–53.8%), surgery (6.7–39%), and age >65 (19.2–33.3%) (Table 2). A significant difference in the number of risk factors was noted between the groups ($p = 0.037$); however, this difference was not present after Bonferroni correction.

Table 2. Risk factors for VTE development

	Heparin $n=154$	Enoxaparin $n=26$	Fondaparinux $n=9$
Number of risk factors (Mean ± SD)	3.3 ± 1.0	3.8 ± 1.0	3.3 ± 1.3
		No. of patients (%)	
Risk factors			
Obesity	36 (23.4)	14 (53.8)	2 (22.2)
Surgery	60 (39)	12 (46.2)	6 (6.7)
Age	41 (26.6)	5 (19.2)	3 (33.3)
CHF	5 (3.2)	1 (3.8)	1 (11.1)
Estrogen	8 (5.2)	4 (15.4)	
Chemotherapy	13 (8.4)		
Tamoxifen	1 (0.6)		
Prior VTE	4 (2.6)	4 (15.4)	
Infection	5 (3.2)	3 (11.5)	
Lung disease	23 (14.9)	3 (11.5)	

Endpoints

Venous thromboembolism events. Three symptomatic VTE events were experienced throughout the study, including two while a patient was admitted and one within 1 month of hospital discharge. All were DVTs and no patients experienced a PE. No differences between groups in the VTE rate were present; however, all VTEs observed occurred in the heparin group (Table 3). All patients who experienced a VTE were male with an average of 3.33 risk factors. One patient with nonsmall cell lung cancer developed a DVT within 3 days of hospital admission while on heparin 5000 units every 8 h. Another patient with pancreatic cancer experienced two DVTs. The first event occurred within 2 days of admission after starting prophylactic heparin 5000 units every 8 h and the second event occurred within 4 weeks from discharge which was unrelated to the initial DVT. The patient did not receive anticoagulant treatment for the initial DVT based on an overall unfavorable risk/benefit ratio.

Safety. Major and minor bleeding rates did not differ between the groups; however, major bleeding was only experienced by those on heparin (2.6%) and included two gastrointestinal bleeding events and one post-operative bleeding event and one patient experienced hematemesis with >2 g/dL drop in hemoglobin. All four experiencing a major bleed required transfusion support. Bleeding rates (major and minor) observed in these three groups were

Table 3. VTE events and bleeding

	Heparin $n=154$	Enoxaparin $n=26$	Fondaparinux $n=9$
	No. of patients (%)		
VTE during admission			
DVT	2 (1.3)	0	0
PE	0	0	0
VTE within 1 month of discharge			
DVT	1 (0.6)	0	0
PE	0	0	0
Total VTE			
DVT	3 (1.9)	0	0
PE	0	0	0
Major bleeding	4 (2.6)	0	0
Minor bleeding	22 (14.3)	3 (11.5)	2 (22.2)
Total bleeding	26 (16.9)	3 (11.5)	2 (22.2)

11.5–22.2% (Table 3). No patients experienced heparin-induced thrombosis (HIT).

DISCUSSION

Despite the increased risk for VTE in cancer, pharmacologic prophylaxis effectively prevented VTEs in the study population. Overall, symptomatic VTEs were uncommon (1.6%) in this retrospective study and complications due to the prophylactic anticoagulant were infrequent and manageable. Minor bleeding was experienced by a reasonable proportion of patients (14% of the total population), and only 2.1% developed a major bleed while on prophylactic anticoagulation.

Prophylactic anticoagulants have demonstrated efficacy in other studies; however, in the cancer population, this has largely consisted of subgroup analyses. Of the entire medically ill population enrolled in VTE prophylaxis trials, only 4.5–20.9% were cancer patients.[4–8] Despite this, pharmacologic VTE prophylaxis has demonstrated efficacy, even in this small subgroup. In the MEDENOX trial, the VTE rate among cancer patients ($n=72$; 12.4% of enrolled patients) was decreased from 19.5% in the placebo group to 9.7% in the enoxaparin group.[4] Another study showed heparin 5000 units every 12 h was not different from the control group in reducing the fatal PE rate in a general medical population; however, a meta-analysis has shown that heparin 5000 units every 8 h was equivalent to LMWH in decreasing DVTs.[7,8] For this reason major guidelines recommend heparin 5000 units every 8 h, which is consistent with the dose the majority of the patients in this analysis received.

More evidence is available to support the use of VTE prophylaxis in the cancer population undergoing surgery.[9–15] Heparin, enoxaparin, dalteparin, and fondaparinux have all been evaluated in this setting with 28–100% of the study population having a cancer diagnosis.[10–14] In the surgical setting, VTE rates among those receiving prophylaxis ranges from 4.7 to 18%.[10–14] The 1.6% VTE rate experienced in this study is lower than that described in other studies, although the present study only evaluated symptomatic VTEs.

The patients in the enoxaparin group in this study differed from the other groups in that the majority of these patients were gynecological oncology patients. This is not surprising as many of these patients were undergoing abdominal surgery and many of the studies evaluating VTE prophylaxis in this setting utilized a LMWH.[11–15] Additionally, many of these patients (53.8%) were obese. Limited evidence exists on the adequate prophylactic dose of LMWH in the obese population; however, given the lack of an increase in VTEs in this group, the standard 40 mg daily dose may be adequate. Nevertheless, this subgroup is too small to draw any firm conclusions.

Though risk factors have been described in the literature, to our knowledge no data is available on the average risk level of patients with cancer. In the general population, almost all hospitalized patients have at least one risk factor for VTE development; however, only 40% have ≥ 3 risk factors.[1] Patients included in this study had 3–4 major risk factors for VTE per admission, and 79% had ≥ 3 risk factors besides their active cancer diagnosis. This is significant and underscores the difference in risk between the general and cancer populations. The increased risk observed in this study highlights the importance of VTE prophylaxis in the cancer population. Moreover, 41.3% of the entire study population underwent surgery without an increase in bleeding with prophylactic anticoagulants. Prior studies have documented major bleeding rates of 0.2–4.1% and minor bleeding rates of 1–14.6% and bleeding rates documented in this report (major: 2.1%; minor: 14%) fall within these ranges.[5,6,11–14]

This study is limited by its size and the disparity in size between groups. VTEs and major bleeding events were only observed in the heparin group; however, this may be a result of the size of the heparin group compared to the other groups. Additionally, the retrospective nature of this project limits the conclusions, which can be drawn from the data. It is possible that all bleeding events may not have been

documented in the patients' charts, which may be particularly true in tracking minor bleeding. Despite this, bleeding rates were similar between groups. The 1-month VTE rate may also be underestimated, as these events may not have been documented in the medical record, especially if the patient presented to another facility outside of our health care system.

CONCLUSION

The majority of patients in this study received heparin prophylaxis; however, gynecological oncology patients were more likely to receive enoxaparin, which may be due to the number of intra-abdominal surgeries in this population. On average, there were 3–4 risk factors for VTE per admission (besides active cancer diagnosis) and according to this analysis pharmacologic prophylaxis is effective at reducing this risk of developing VTE. Though there were more VTE and major bleeding events in the heparin group, a statistically significant difference was lacking. This increased VTE and major bleeding rate may be due to the size of the heparin group; however further research is necessary to evaluate this observation.

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