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Venous thromboembolism (VTE) rates following the implementation of extended duration prophylaxis for patients undergoing surgery for gynecologic malignancies

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Abstract

Objective—To compare the incidence of venous thromboembolism (VTE) before and after the implementation of standardized extended duration prophylaxis guidelines in women undergoing laparotomy for gynecologic cancer.

Methods—In October 2009, departmental practice guidelines were implemented for VTE prevention. Patients undergoing laparotomy for gynecologic cancer were started on low molecular weight heparin (LMWH) within 24 hours of surgery and it was continued for a total of 28 days postoperatively. The incidence of VTE diagnosed within 30 and 90 days of surgery was determined and compared to a historic cohort of patients who underwent surgery prior to implementation of the guidelines.

Results—The incidence of VTE within 30 days of surgery decreased from 2.7% (8/300) to 0.6% (2/334) following implementation of VTE prevention guidelines (78% reduction, p=0.040). However, when the pre and post-guideline implementation groups were compared for the development of VTE within 90 days of surgery, there was no significant difference (11/300 (3.7%) vs. 10/334 (3.0%) respectively, p=0.619). The median time between surgery and VTE diagnosis was 12 days in the pre-guideline implementation group, compared with 57 days in the post-guideline implementation group (p=0.012).

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Conclusion—Patients receiving extended duration LMWH were found to have significantly lower rates of VTE within 30 days of surgery when compared with similar patients who did not receive extended duration LMWH. However, this effect was not sustained when the groups were compared for VTE diagnosis within 90 days of surgery. Additional study is needed to further reduce long-term VTE rates in this high-risk population.

Introduction

Venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolus (PE) is the most common preventable cause of hospital death in the United States [1-3]. Women undergoing major surgery for gynecologic cancer are at significant risk for developing a VTE due to the combination of pelvic surgery and underlying malignancy [3-5]. This risk can be significantly reduced with pharmacologic prophylaxis consisting of subcutaneous unfractionated heparin or low-molecular weight heparin (LMWH) in addition to mechanical prophylaxis [3, 6]. The prevention of VTE has become a nationwide patient safety goal [7].

Evidence-based guidelines regarding VTE prophylaxis are available from The American College of Chest Physicians (ACCP) [3], The American Society of Clinical Oncology (ASCO) [8], The National Comprehensive Cancer Network (NCCN) [9], and The American College of Obstetrics and Gynecology (ACOG) [10]. All the above guidelines recommend that patients undergoing abdominal or pelvic surgery for malignancy receive pharmacologic prophylaxis, with consideration of continuation for up to 28 days postoperatively. Of note, the recently updated 2012 guidelines from the ACCP include a more definitive recommendation of VTE prophylaxis continuation for a total of 28 days postoperatively, having previously recommended “up to 28 days” in this high risk population [3]. Despite clear recommendations from evidence-based guidelines, VTE prophylaxis is widely underused in women undergoing surgery for gynecologic cancer [11-13]. Possible deterrents include concern for bleeding complications, cost or unfamiliarity with current practice guidelines.

In 2009, we investigated what appeared to be a higher than expected postoperative VTE rate among our gynecologic oncology patients. We noted poor compliance with existing VTE prevention guidelines. There was inconsistent use of postoperative inpatient pharmacologic prophylaxis and patients were not being discharged on extended duration pharmacologic prophylaxis. These findings prompted us to enact standardized departmental-wide VTE prophylaxis practice guidelines for all patients undergoing laparotomy for gynecologic cancer. The objective of this study was to compare the incidence of VTE before and after the implementation of these standardized VTE prophylaxis guidelines.

Materials & Methods

In October 2009, the Department of Gynecologic Oncology at The University of Texas MD Anderson Cancer Center initiated a quality improvement project to improve adherence to national VTE prophylaxis guidelines, with the overall goal to significantly reduce postoperative VTE rates. A multidisciplinary team including physicians, nurses, and pharmacists was formed. A departmental clinical retreat was held to review the incidence and prevalence VTE data, educate the stakeholders (faculty, trainees, nurses and pharmacists) as to the safety and efficacy of existing guidelines, and to reach consensus regarding a standardized VTE prevention policy to raise guideline compliance. Practice guidelines were implemented and all patients with a gynecologic malignancy undergoing laparotomy were initiated on LMWH within 24 hours of surgery and it was continued for a total of 28 days postoperatively. Post-operative order sets were updated for patients to

automatically receive enoxaparin 40 mg subcutaneously every 24 hours, beginning at 9:00 am on postoperative day number one, provided the hemoglobin ≥ 9 grams/dL and platelet count ≥ 100,000/mm^3. If these parameters were not met, the nurse was required to notify the physician to determine whether the enoxaparin should still be administered. Dosing adjustments were made for renal insufficiency and morbid obesity. Patients with a BMI ≥ 50 kg/m^2 received 40 mg of enoxaparin every 12 hours. For patients with epidural catheters, the LMWH dose was held on the morning of removal and restarted four hours after the catheter was pulled. All patients also received mechanical prophylaxis with graduated compression stockings and sequential compression devices (SCDs), initiated in the operating room prior to surgery and continued until hospital discharge. The use of pre-operative pharmacologic prophylaxis was not included in the guidelines, as consensus on this topic could not be reached among the gynecologic oncology faculty.

Our study population comprised all patients undergoing exploratory laparotomy for gynecologic cancer. Patients with benign disease on final pathology and patients with an existing VTE at the time of surgery were excluded. Patients undergoing minimally invasive surgery were also excluded due to the low rates of VTE previously reported in this population [14]. Patient education regarding VTE prophylaxis was initiated by the outpatient nursing staff at the pre-operative visit. Following surgery, the clinical pharmacists and inpatient nursing staff instructed the patients and their caretakers on the administration of LMWH at home. Patients were contacted by telephone upon completion of therapy by the clinical pharmacy team to determine adherence. Patients responded to a brief questionnaire regarding missed doses, timing of administration, and adverse effects. The study was approved by the Institutional Review Board of the University of Texas MD Anderson Cancer Center in 2009. A waiver of informed consent was obtained.

Patient information including demographic data and clinical information was abstracted from the medical record. Data regarding doses and duration of treatment with LMWH therapy, medication adherence, and any complications associated with LMWH therapy during hospitalization were recorded. Medical records were reviewed for the development of a VTE, defined as DVT or PE confirmed by imaging. All imaging studies performed were for symptoms or for routine assessment as part of their cancer treatment. Routine imaging was not performed to specifically detect VTE in asymptomatic patients. We tracked the incidence of VTE within 90 days of surgery and stratified their occurrence as within 30 days and within 90 days of surgery. The incidence of VTE was compared to a historic cohort of consecutive patients who underwent surgery prior to implementation of the guidelines. In this pre-guideline implementation cohort, all patients received mechanical prophylaxis but pharmacologic prophylaxis measures were inconsistent and did not include extended duration LMWH.

Demographic and clinical characteristics were summarized using descriptive statistics. The Wilcoxon test and Fisher's exact test were used to compare demographic and clinical factors, as well as VTE rates before and after implementation of the prevention guidelines. These tests were also used to compare demographic and clinical factors between patients who developed a VTE to those patients who did not. All p-values are 2-sided, and were considered significant if <0.05. All analyses were performed using SAS 9.1 for Windows (Copyright © 2002-2003 by SAS Institute Inc., Cary, NC) and StatXact-7© for Windows (Copyright © 2005, 1989-2005, Cytel Software Corporation, Cambridge, Massachusetts).

Results

Following implementation of the VTE prophylaxis guidelines, 334 consecutive patients underwent laparotomy for gynecologic cancer between October 2009 and April 2011 (post-

guideline implementation group). These patients were compared to 300 consecutive patients who underwent laparotomy for gynecologic cancer between July 2005 and December 2006 (pre-guideline implementation group). Demographic and clinical factors are compared between the two groups in Table 1. There were no significant differences in median age at surgery, BMI, or estimated blood loss (EBL). However, the group treated after implementation of the new guidelines had a higher rate of ovarian cancer (p=0.010), longer median anesthesia time (p=0.009), and a longer median length of hospital stay (LOS) (p=0.002).

Prior to implementation of the VTE prophylaxis guidelines, a VTE was diagnosed within 30 days of surgery in 8 of 300 patients (2.7%) compared with 2 of 334 patients (0.6%) following implementation of the guidelines (78% reduction in VTE, p=0.040) (Table 2). However, when the pre and post-guideline implementation groups were compared for the development of VTE within 90 days of surgery, there was no significant difference (11/300 (3.7%) vs. 10/334 (3.0%) respectively, p=0.619). The median time between surgery and VTE diagnosis was 12 days (range 1 to 84) in the pre-guideline implementation group, compared with 57 days (range 13 to 86) in the post-guideline implementation group (p=0.012). Eighty-two percent of patients in the pre-guideline implementation group and 70% of patients in the post-guideline implementation group who developed a VTE were symptomatic, presenting with either lower extremity swelling or shortness of breath. The remaining patients were asymptomatic and the VTE was diagnosed on routine imaging with computed tomography (CT) scan. There were two VTE related deaths, one in the pre-guideline implementation group and one in the post-guideline implementation group.

In the post-guideline implementation group, all patients (100%) received prophylaxis with LMWH during hospitalization. However, only 278 patients (83.2%) started the LMWH within 24 hours of surgery. It was started on postoperative day #2 in 33 patients (9.9%), on postoperative day #3 in 16 patients (4.8%), and it did not begin until postoperative day #4 or later in 7 patients (2.1%). In the majority of cases, the initiation of LMWH was delayed due to significant intraoperative or postoperative bleeding and/or laboratory values not meeting the parameters set forth in our guidelines (hemoglobin ≥ 9 grams/dL and platelet count ≥ 100,000/mm^3). Preoperative LMWH was not routinely given in either group.

Table 3 compares characteristics between patients who developed a VTE and patients who did not in the pre-guideline implementation group. There were no statistically significant differences between patients who did and did not develop VTE with respect to age, cancer type, time under anesthesia, estimated blood loss, or LOS. Table 4 compares characteristics between patients who developed a VTE and patients who did not in the post-guideline implementation group. VTE was associated with a delay in initiating LMWH (>24 hours from surgery), with the mean time between surgery and LMWH initiation equal to 1.9 days in the patients who developed a VTE compared to 1.3 days in the patients without a VTE (p=0.35). VTE was also associated with a lower median body mass index (24.5 vs. 28.9 kg/m^2, p=0.020). There was no association between VTE and age, cancer type, time under anesthesia, estimated blood loss, or LOS.

All patients in the post-guideline implementation group were contacted to determine adherence with extended duration LMWH. Seventy-nine percent of patients reported completing the entire 28-day course of LMWH. In patients who did not complete all doses, the majority (83%) missed only one to five doses. Bruising (49%) and pain at injection site (21%) were the most common side effects, with no serious adverse events noted. No VTEs were diagnosed among any of the patients who did not complete the 28-day course of LMWH.

Discussion

In this study we found that compliance with established VTE prevention recommendations could be positively affected by our awareness and the implementation of standardized departmental guidelines. Enactment of these guidelines significantly lowered the rate of VTE diagnosed within 30 days of surgery in women undergoing laparotomy for gynecologic cancer compared with similar patients not receiving extended duration LMWH (0.6 vs. 2.7%, respectively, p=0.040). However, this effect was not sustained when the groups were compared for VTE diagnosed within 90 days of surgery (3.0 vs. 3.7%, respectively, p=0.619). The median time between surgery and VTE diagnosis was significantly longer in the group that received extended duration VTE prophylaxis compared with group that did not (57 vs. 12 days, respectively, p=0.012).

Despite clear recommendations from evidence-based guidelines, VTE prophylaxis is underused in women undergoing surgery for gynecologic cancer. Martino *et al.* [11] surveyed 343 members of the Society of Gynecologic Oncologists (SGO) regarding practice patterns of perioperative VTE prophylaxis in patients with gynecologic cancer. Although all respondents reported using some form of VTE prophylaxis, only 42% of respondents used a combination of mechanical and pharmacologic prophylaxis. Furthermore, only 11% of respondents reported prescribing extended duration pharmacologic prophylaxis after patient discharge [11].

A subsequent study by Wright *et al.* [12] utilized the commercially available *Perspective* database to evaluate VTE prophylaxis among 738,150 women undergoing gynecologic surgery. The *Perspective* database includes information from over 500 acute-care hospitals in the United States. The authors reported that 46.6% of women used mechanical prophylaxis alone, 5.5% pharmacologic prophylaxis alone, and 8.4% used a combination of mechanical and pharmacologic prophylaxis. No prophylaxis was used in 39.6% of women [12]. In a related study, the same authors examined VTE prophylaxis rates among 252,950 patients undergoing oncologic surgery for various types of malignancy [13]. They noted that some form of prophylaxis was given to 79% of patients, but only 46% of patients received pharmacologic prophylaxis. In both studies, appropriate VTE prophylaxis was associated with treatment by high-volume surgeons and at high-volume hospitals [12, 13].

The optimal duration for postoperative VTE prophylaxis remains unclear. The randomized placebo-controlled trial, Enoxaparin and Cancer (ENOXACAN II) evaluated the safety and efficacy of extended duration enoxaparin in patients undergoing surgery for multiple types of malignancy [15]. Enoxaparin was given to all patients preoperatively and continued for 6 to 10 days following surgery. Patients were then randomly assigned to placebo or enoxaparin for a total of 27 to 31 days postoperatively. Similar to our study findings, the VTE rate within 31 days of surgery was significantly lower in the extended duration enoxaparin group (4.8%) compared with the placebo group (12%), for a relative risk reduction of 60%. The majority of patients were asymptomatic with VTE diagnosed on routine venography performed as part of the trial between post-operative days 25 and 31. However, in contrast with our study findings, there remained a sustained decrease in VTE rates at 90 days in the extended duration enoxaparin group compared with the placebo group (5.5 vs. 13.8%, respectively) [15].

In our cohort, the median time between surgery and VTE diagnosis was 12 days in the pre-guideline implementation group not receiving extended duration LMWH. However, this interval increased to 57 days in the post-guideline implementation group receiving extended duration LMWH. Although the VTE rate within 30 days of surgery was significantly lower in the post-implementation group, this effect was lost when the two groups were compared

for VTE development within 90 days of surgery. It remains unclear if extended duration LMWH delayed the time to VTE development and diagnosis or if other factors such as the initiation of chemotherapy led to the later diagnosis of VTE.

In a similar study, Peedicayil *et al.* [16] retrospectively evaluated VTE rates among a cohort of 4,158 women who underwent major surgery for gynecologic cancer. They noted that 76% of VTEs were diagnosed more than seven days following surgery, and that 36% occurred after more than four weeks. In their study, hospital stay ≥ 5 days and prior VTE were identified as significant risk factors for the development of postoperative VTE. Based on the findings from our study and others, it remains unclear what the optimal duration is for postoperative pharmacologic VTE prophylaxis in patients with gynecologic malignancies. It is also uncertain if patients with additional risk factors such as residual disease or adjuvant chemotherapy require a more prolonged course of VTE pharmacologic prophylaxis. Interestingly, several recent studies have shown a significant reduction in VTE rates with LMWH in ambulatory patients receiving chemotherapy for a variety of malignancies [17, 18]. Further study is needed to better identify specific VTE risk factors in this population in order to better stratify patients and determine the optimal duration of prophylaxis based on these factors.

Several studies have evaluated the cost effectiveness of VTE prophylaxis. It is estimated that the mean cost of VTE treatment is $20,000 per event [7]. Teoh *et al.* [19] recently described a decision model comparing the cost effectiveness of six VTE prophylaxis strategies for women following laparotomy for ovarian cancer. These included: 1) no thromboprophylaxis; 2) inpatient sequential compression devices (SCDs) alone; 3) inpatient unfractionated heparin (UFH) alone; 4) inpatient LMWH alone; 5) inpatient UFH followed by extended duration outpatient UFH for a total of one month postoperatively; and 6) inpatient LMWH followed by extended duration outpatient LMWH for a total of one month postoperatively. Inpatient UFH followed by extended duration outpatient UFH for a total of one month postoperatively was the least expensive, yet most effective strategy. Inpatient LMWH followed by extended duration outpatient LMWH for a total of one month postoperatively was equally effective, yet more expensive [19]. These findings support the practice of using extended duration LMWH for 28 days postoperatively. Although UFH has been shown to be more cost-effective, the requirement for multiple injections daily compared with the once daily administration of LMWH would potentially result in decreased compliance.

A subsequent study by Uppal *et al.* [20] used a Markov decision model to investigate the cost-effectiveness of four weeks of enoxaparin in patients undergoing primary debulking surgery for stage IIIC ovarian cancer. They estimated the incremental cost per quality-adjusted life-year (QALY) to be $5,236 and $−1,462 at one and five years respectively. Furthermore, they estimated a 12% reduction in clinically evident VTE episodes [20]. A related potential deterrent to extended duration LMWH is the perceived or actual costs incurred by the patient. Our group recently reported the patient associated costs associated with outpatient LMWH for a total of 28 days following surgery [21]. In our cohort, the mean patient cost to complete 28 days of enoxaparin was $62 (median $21, range $0 to $1,210). The mean cost was $102 for patients with Medicare, $62 for patients with private insurance, and $1 for patients with Medicaid. Furthermore, a decrease in the mean patient cost was observed after the approval of generic enoxaparin by the Food and Drug Administration in July 2011. Approximately 10% of patients required prior authorization from their insurance company to fill the prescription [21].

Our study is limited in that while the guidelines were enacted prospectively in 2009, we did not provide specific guidance for VTE assessment (other than clinical suspicion or as an

incidental finding on routine imaging). In addition, our data collection methods varied, with the information on the pre-implementation group collected retrospectively and the post-implementation group collected prospectively. The study consists of a single institution experience, which has a large cancer referral base and may lack external validity. Furthermore, we used follow-up assessment time periods of 30 and 90 days, and it remains unclear if the cases of VTE were due to surgical or nonsurgical causes such as residual disease, progressive cancer or administration of chemotherapy. In addition, patient follow-up was not standardized potentially leading to detection bias. The post-guideline implementation group had higher rates of ovarian cancer, median anesthesia time and median LOS compared with the pre-guideline implementation group, potentially contributing to the similar VTE rates at 90 days despite extended duration LMWH. We also did not routinely administer pre-operative pharmacologic prophylaxis, as consensus on this topic could not be reached among the gynecologic oncology faculty. Despite these limitations, the study included a large cohort of patients and achieved a 79% patient-reported adherence rate with the recommended 28-day regimen of LMWH. In response to the observations in this study, our department has incorporated the use of extended-duration VTE pharmacologic prophylaxis as a permanent measure of good clinical practice.

In summary, extended duration LMWH was found to be safe and effective, and resulted in a significant decrease in VTE incidence within 30 days of surgery in our cohort of women undergoing laparotomy for gynecologic malignancy. However, this effect was not sustained when the groups were compared for VTE diagnosis within 90 days of surgery. Further prospective trials are needed to better define VTE risk factors in this population and to determine the optimal duration of VTE pharmacologic prophylaxis in women undergoing major surgery for gynecologic cancer.

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Research Highlights

- Venous thromboembolism rates within 30 days of surgery were significantly reduced in gynecologic cancer patients receiving extended duration prophylaxis
- The decrease in venous thromboembolism rates was not sustained at 90 days following surgery
- Additional study is needed to further reduce long-term venous thromboembolism rates in women with gynecologic malignancies

Table 1

Comparison of demographic and clinical information between the patients undergoing surgery pre and post-implementation of the VTE prophylaxis guidelines

Characteristic	Pre-implementation (n=300)	Post-implementation (n=334)	p-value
Age at diagnosis (years):			
Mean (SD *)	58 (13.5)	57 (12)	0.175
Median (Range)	60 (20-88)	58 (20-85)	
Body mass index (kg/m^2):			
Mean (SD)	29.5 (8.7)	30.1 (7.8)	0.076
Median (Range)	27.4 (15.6-62.9)	28.8 (16.0-63.4)	
Cancer type (N (%)):			
Ovary	151 (50.3%)	203 (60.8%)	0.010
Uterine	112 (37.3%)	89 (26.6%)	
Cervix	32 (10.7%)	30 (9.0%)	
Vagina/Vulva	5 (1.7%)	12 (3.6%)	
Anesthesia time (minutes):			
Mean (SD)	286 (121)	310 (140)	0.009
Median (Range)	263 (78-827)	289 (74-1099)	
Length of stay (days):			
Mean (SD)	8 (6)	7 (4)	0.002
Median (Range)	5 (1-50)	6 (2-31)	
Estimated blood loss (ml):			
Mean (SD)	523 (603)	466 (513)	0.230
Median (Range)	350 (10-5000)	300 (10-4500)	

* SD: standard deviation

Table 2
VTE rates pre and post-implementation of the VTE prophylaxis guidelines

	Pre-implementation (n=300)	Post-implementation (n=334)	p-value
VTE within 30 days of surgery	8 (2.7%)	2 (0.6%)	0.040
VTE within 90 days of surgery	11 (3.7%)	10 (3.0%)	0.619
Time between surgery and VTE diagnosis (days):			
Mean	20	52	0.012
Median	12	57	
Range	1-84	13-86	
VTE type:			
Pulmonary embolus	7 (63.6%)	5 (50.0%)	0.670
Deep venous thrombosis	4 (36.4%)	5 (50.0%)	

Table 3

Comparison of characteristics between patients developing a VTE and patients not developing a VTE in the pre-implementation group

Characteristic	No VTE (n=289)	VTE (n=11)	p value
Age (years):			
Mean (SD *)	58 (13.4)	54 (17.1)	0.512
Median (Range)	60 (35-88)	58 (22-78)	
Body mass index (kg/m^2):			
Mean (SD)	29.6 (8.8)	27.4 (5.8)	0.603
Median (Range)	27.4 (16.9-62.9)	27.5 (19.2-37.1)	
Cancer type (N (%)):			
Ovary	148 (51.2%)	3 (27.2%)	0.080
Uterine	108 (37.4%)	4 (36.4%)	
Cervix	28 (9.7%)	4 (36.4%)	
Vagina/Vulva	5 (1.7%)	0 (0.0%)	
Estimated blood loss (ml):			
Mean (SD)	521 (598)	565 (758)	0.371
Median (Range)	350 (10-5000)	100 (25-2500)	
Anesthesia time (minutes):			
Mean (SD)	284 (118)	330 (182)	0.438
Median (Range)	263 (90-827)	355 (120-789)	
Length of stay (days):			
Mean (SD)	7.4 (5.9)	11.2 (11.5)	0.293
Median (Range)	5.0 (4.0-50.0)	7.0 (1.0-40.0)	
LMWH start (postoperative day):			
Mean (SD)	Not available	Not available	
Median (Range)			

* SD: standard deviation

Table 4

Comparison of characteristics between patients developing a VTE and patients not developing a VTE in the post-implementation group

Characteristic	No VTE (n=324)	VTE (n=10)	p value
Age (years):			
Mean (SD *)	57.2 (12.3)	52.8 (13.0)	0.292
Median (Range)	58 (20-85)	55.5 (33-70)	
Body mass index (kg/m^2):			0.020
Mean (SD)	30.3 (7.8)	24.9 (4.3)	
Median (Range)	28.9 (16.0-63.4)	24.5 (17.9-31.0)	
Cancer type (N (%)):			
Ovary	197 (60.8%)	6 (60%)	0.220
Uterine	88 (27.2%)	1 (10%)	
Cervix	28 (8.6%)	2 (20%)	
Vagina/Vulva	11 (3.4%)	1 (10%)	
Previous VTE:			
Yes	7 (2.2%)	0 (0%)	0.999
No	317 (97.8%)	10 (100%)	
Estimated blood loss (ml):			
Mean (SD)	459.4 (498.9)	696.0 (857.8)	0.859
Median (Range)	300.0 (10.0-4500.0)	287.5 (10.0-2200.0)	
Anesthesia time (minutes):			
Mean (SD)	294 (138)	336 (234)	0.872
Median (Range)	270 (66-1092)	318 (90-900)	0.404
Length of stay (days):			
Mean (SD)	7.1 (3.6)	7.9 (3.4)	
Median (Range)	6.0 (2.0-31.0)	7.0 (5.0-14.0)	
LMWH start (postoperative day):			
Mean (SD)	1.3 (0.9)	1.9 (1.4)	0.035
Median (Range)	1.0 (0.0-12.0)	1.0 (1.0-5.0)	

* SD: standard deviation