Incidence and Prevention of Venous Thromboembolism in Patients Undergoing Breast Cancer Surgery and Treated According to Clinical Pathways

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Objective: To minimize treatment variations, we have implemented clinical pathways for all breast cancer patients undergoing surgery. We sought to determine the incidence of postoperative venous thromboembolism (VTE) in patients treated on these pathways.

Summary Background Data: Cancer patients have an increased risk of VTE because of a hypercoagulable state. The risk of VTE following breast cancer surgery is not well established.

Methods: We retrospectively reviewed prospectively collected data for all patients who underwent breast cancer surgery and were treated on the clinical pathways with mechanical antiembolism devices and early ambulation in the postoperative period between January 2000 and September 2003.

Results: During the study period, 3898 patients underwent 4416 surgical procedures. Seven patients with postoperative VTE within 60 days were identified, for a rate of 0.16% per procedure. Six patients presented with only a deep venous thrombosis or a pulmonary embolism; 1 patient had both. The median time from surgery to diagnosis of VTE was 14 days (range, 2–60 days; mean, 22 days). No relationship was identified between stage of breast cancer or type of breast surgery and development of VTE. Two (29%) of the 7 patients with VTE had received neoadjuvant chemotherapy. VTE treatment consisted of subcutaneous low-molecular-weight heparin (n = 5) or intravenous heparin (n = 2) followed by warfarin. There were no deaths.

Conclusions: VTE following breast cancer surgery is rare in patients who are treated on clinical pathways with mechanical antiembolism devices and early ambulation in the postoperative period. We conclude that systemic VTE prophylaxis is not indicated in this group of patients.

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Venous thromboembolism (VTE), which includes both deep venous thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity and mortality in patients with cancer.[1] The estimated annual incidence of a first episode of VTE in the general population is 0.117%.[2] Patients with cancer have a 4-fold increased risk of VTE, for an annual incidence of approximately 0.48%.[3] This increased risk of VTE is greater in some cancers than in others. Sorensen et al,[4] in a large population-based study of over 26,000 patients with primary VTE, observed a strong association between VTE and a subsequent diagnosis of pancreatic, brain, or primary liver cancer but not breast cancer. The mechanisms responsible for the increased risk of VTE in cancer are poorly understood but are thought to be due to the hypercoagulable state of malignancy.[5]

Cancer patients are also at increased risk of developing VTE because of the cancer treatments delivered, including surgery, chemotherapy, hormonal therapy, radiotherapy, and use of indwelling central venous catheters.[6] Patients undergoing cytotoxic and hormonal therapy for breast cancer can have VTE rates as high as 9%.[7] Cancer patients undergoing surgical procedures have at least twice the risk of postoperative DVT and more than 3 times the risk of fatal PE compared with patients without cancer undergoing similar procedures.[8] The incidence of venographically proven DVT in cancer patients undergoing surgery ranges from 20% to 40%, and the risk of a fatal PE is approximately 1%.[9] The risk of postoperative VTE can be reduced through prophylactic measures such as administration of low-dose heparins and use of graded antiembolism elastic compression stockings and pneumatic compression devices.[9]

The risk of VTE in patients undergoing surgery for abdominal and pelvic cancers is established, as are the recommendations for VTE prophylaxis in such patients.[9] However, the risk of VTE in patients undergoing surgery for breast cancer is not clear, and the recommendations for VTE prophylaxis in these patients are not well established. In a recent survey in the United Kingdom of 126 surgeons performing breast surgery, 38 surgeons (30%) did not routinely administer thromboprophylaxis, since the majority considered breast cancer patients to be at low risk for thromboem-

bolic complications. The estimated incidence of VTE after breast surgery in that survey was less than 1%.[10]

We have developed and implemented clinical pathways for all patients undergoing surgery for breast cancer to minimize treatment variations and to provide a standard prophylactic regimen for VTE. The objective of this study was to determine the incidence of VTE within 60 days after surgery in patients treated on these pathways.

PATIENTS AND METHODS

Clinical Pathways for Breast Surgery

At the University of Texas M.D. Anderson Cancer Center, patients undergoing surgery for known or presumed breast cancer are treated on clinical pathways to minimize variation in treatment. Patients receive preoperative teaching about the importance of immediate postoperative ambulation and the use of knee-length antiembolism elastic compression stockings (T.E.D. stockings, Kendall Healthcare, Mansfield, MA) and calf-length intermittent pneumatic compression devices (SCD Sequential Compression System Intermittent Pneumatic Compression, Kendall Healthcare). The antiembolism elastic stockings and intermittent pneumatic compression devices are applied before anesthesia is induced. When patients have recovered from anesthesia, they are mobilized early, and nursing staff and physiotherapists help them walk as needed. Most patients undergoing breast-conserving surgery are discharged home the day of surgery. Patients undergoing total mastectomy and axillary lymph node dissection are observed in the hospital overnight and discharged the next morning. Patients undergoing immediate breast reconstruction stay in the hospital 2 to 6 days. While in the hospital, patients are encouraged to ambulate as frequently as possible. While in bed, patients wear the calf-length intermittent pneumatic compression devices and knee-length antiembolism elastic stockings. When patients are discharged home, they are encouraged to walk as much as possible and to wear the antiembolism elastic stockings when resting, until they are fully active.

Patients and Diagnosis of VTE

Patients with known or presumed breast cancer who underwent breast surgery between January 1, 2000, and September 30, 2003, and were treated on the breast surgery clinical pathways were the subjects of this institutional review board-approved study. Several databases were queried to identify cases of VTE within 60 days after surgery among these patients. The institutional prospective breast cancer database was queried for all patients with a diagnosis of DVT or PE. The medical records database was queried for patients with ICD-9-CM codes for DVT or PE and any breast operation. The radiology database was queried for breast cancer patients undergoing duplex Doppler sonography, ventilation-perfusion scans, computerized tomography of the chest and lungs, computerized pulmonary angiography, or venography. To further identify patients with postoperative VTE, the pharmacy database was searched for patients who underwent breast surgery and received pharmacologic treatment with warfarin, unfractionated heparin, or low-molecular-weight heparins (LMWH). The following patient data were collected for patients with VTE: age, sex, type and length of surgical procedure, stage of breast cancer, site of DVT or PE, method of diagnosis of VTE, method of treatment of VTE, and types of neoadjuvant or adjuvant chemotherapy, hormonal therapy, and radiotherapy administered.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel (version 2002, Microsoft Corporation, Redmond, WA). For comparison between treatment groups in the distribution of continuous variables, a 2-tailed Student *t* test was used. Differences were considered to be significant if the 2-tailed *P* value was less than 0.05.

RESULTS

During the study period, 3898 patients underwent 4416 surgical procedures for established or suspected breast cancer. The majority of patients (74.2%) were white (Table 1). The median age at the time of surgery was 54.4 years (range, 11–91.8 years). Segmental mastectomy (lumpectomy) with intraoperative lymphatic mapping and sentinel lymph node biopsy was the most commonly performed procedure (Table 2). Approximately 18% of patients underwent immediate breast reconstruction with tissue expanders, tunneled flaps, or free flaps. The median operative time for patients who underwent immediate breast reconstruction was 442 minutes (range, 74–1104 minutes; mean, 466 minutes); the median operative time for patients who did not undergo immediate reconstruction was 117 minutes (range, 9–585 minutes; mean, 125 minutes). The difference between these 2 groups was statistically significant ($P < 0.001$).

Seven patients, all of whom received a general anesthetic and all women, developed VTE within 60 days following surgery, for a rate of 0.16% per procedure. Details for these patients are presented in Table 3. The median time from surgery to diagnosis of VTE was 14 days (range, 2–60 days; mean, 22 days). Three patients had a DVT only. These patients presented with lower-extremity swelling and/or pain and were diagnosed radiographically. Three patients had a PE only. Two of these presented with dyspnea and pleuritic chest pain; 1 presented with dyspnea only. All 3 had radiographic evidence of a PE. In these 3 patients, duplex Doppler sonog-

TABLE 1. Patient Characteristics

Characteristic	No. of Patients (n = 3898)	% of Patients
Gender		
Female	3871	99.3
Male	27	0.7
Ethnicity		
White	2893	74.2
Hispanic	443	11.4
Black	358	9.2
Other	204	5.2
Age (yr)		
Range	11–91	
Median	54.4	

TABLE 2. Surgical Procedures and Median Procedure Time

Type of Procedure	No. of Procedures (n = 4416)	% of Procedures	Length of Surgery	
			Median (minutes)	Range (minutes)
Breast-conserving surgery				
Excisional breast biopsy	354	8.0	53	9–343
Segmental mastectomy	585	13.3	64	15–457
Segmental mastectomy + ALND	228	5.2	149	71–568
Segmental mastectomy + IOLM + SLNB	984	22.3	118	33–380
Segmental mastectomy + IOLM + SLNB + ALND	129	2.9	180	81–375
Mastectomy				
Mastectomy*	138	3.1	106	27–440
Mastectomy + IOLM + SLNB	231	5.3	141	63–396
MRM	540	12.2	155	55–432
MRM + IOLM + SLNB	158	3.6	181	42–536
Surgery with reconstruction				
Mastectomy + IR	154	3.5	425	104–1103
Mastectomy + IOLM + SLNB + IR	249	5.6	426	74–1104
MRM + IR	271	6.1	452	107–990
MRM + IOLM + SLNB + ALND + IR	112	2.5	464	92–1010
Lymph node evaluation only				
ALND	132	3.0	101	40–377
IOLM + SLNB	66	1.5	71	19–186
Other	85	1.9	102	14–585

*Total mastectomy or skin-sparing total mastectomy.

ALND indicates axillary lymph node dissection; IR, immediate reconstruction; IOLM, intraoperative lymphatic mapping; MRM, modified radical mastectomy or skin-sparing total mastectomy with ALND; SLNB, sentinel lymph node biopsy.

raphy of the lower extremities and, in 1 patient, of the upper extremities failed to reveal any evidence of DVT. One patient had both a DVT and a PE. None of the patients with a PE had a central venous catheter present immediately before surgery or in the postoperative period before diagnosis of a PE. None of the patients with a PE required mechanical ventilatory support.

In addition to the details presented in Table 3, the following further details warrant mention. Patient 2 presented with recurrent breast cancer. Five years earlier, she had undergone a segmental mastectomy and axillary lymph node dissection followed by adjuvant chemotherapy and hormonal therapy but no radiotherapy at another institution. She was still taking tamoxifen at the time of diagnosis of recurrent breast cancer. This medication was discontinued 2 weeks before her undergoing a completion mastectomy with a redo axillary lymph node dissection and immediate breast reconstruction at our institution. She was diagnosed with a PE on postoperative day 11 and treated initially with LMWH and warfarin, and she was treated with maintenance therapy with subcutaneous dalteparin while receiving adjuvant chemotherapy. Patient 3 was morbidly obese, with a body mass index of 46 kg/m^2. Three weeks before undergoing bilateral mastectomies and axillary lymph node dissection for locally advanced breast cancer at our institution, the patient underwent bilateral reduction mammoplasties at another institution and was diagnosed with breast cancer. Following breast cancer surgery at our institution, she was diagnosed with a lower-extremity DVT. At the time of this report, she is undergoing adjuvant chemotherapy and radiotherapy and remains on warfarin 11 months after surgery. Patient 4 presented with postoperative thigh pain and swelling. A duplex Doppler sonogram was negative for a lower-extremity DVT. The patient underwent an infused computed tomography scan of the pelvis and lower extremities, which indicated the presence of a left common and external iliac thrombosis. She was treated with LMWH followed by warfarin, and symptoms resolved.

Two (29%) of the 7 patients diagnosed with postoperative VTE received neoadjuvant chemotherapy for locally advanced breast cancer. One of these, patient 7 (Table 3), developed a PE of unknown origin while receiving neoadjuvant chemotherapy. She was treated with warfarin for 10 weeks. Before surgery, she underwent a duplex Doppler study of the lower extremities, which showed no evidence of a DVT. An inferior vena cava filter was inserted the day before surgery. The patient did not receive anticoagulation therapy after surgery. She presented 60 days after surgery complaining of right-lower-extremity swelling and tenderness. Findings on duplex Doppler sonography were consistent with an above-knee DVT. She was treated with LMWH and then converted to oral warfarin, and symptoms resolved.

The mean operative time in patients who developed VTE was 278 minutes, compared with a mean of 256 minutes in patients who underwent similar surgical procedures and did not develop VTE ($P = 0.7$). The mean operative time in patients who developed VTE was greater than the mean of 186 minutes

TABLE 3. Characteristics of Patients With VTE Within 60 Days After Breast Cancer Surgery

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age at surgery (yr)	48	41	66	45	72	58	66
Breast cancer stage	T1 N0 M0	T2 N0 M0	T2 N1 M0	Tis N0 M0	T1 N0 M0	T4 N1 M0	T4 N1 M0
Procedure	MRM	Mastectomy ALND TRAM	B/L mastectomies Left ALND	B/L mastectomies B/L Lat dorsi flaps Tissue expanders	B/L mastectomies Left SLNB Left ALND	Mastectomy	Segmental mastectomy ALND
VTE diagnosis							
Days after surgery	2	11	13	14	25	29	60
Symptoms and signs	Dyspnea	Dyspnea Chest pain Hypoxia	Calf pain/swelling	Thigh pain/swelling	Dyspnea Chest pain Upper extremity swelling	Dyspnea Chest pain	Thigh and calf pain/swelling
DVT	No	No	Yes	Yes	No	Yes	Yes
PE	Yes	Yes	No	No	Yes	Yes	No
Method of VTE diagnosis							
Ventilation-perfusion scan		Positive				Positive	
CT pulmonary angiography	Positive				Positive	Positive	
Duplex Doppler sonography	Negative	Negative	Positive	Negative	Negative	Positive	Positive
CT of abdomen and pelvis				Positive			
Anticoagulation therapy							
Type	IV heparin Enoxaparin Warfarin	Enoxaparin Warfarin Dalteparin	IV heparin Warfarin	Enoxaparin Warfarin	Enoxaparin IV heparin Warfarin	Enoxaparin Warfarin	Enoxaparin Warfarin
Duration (mo)	12	4	11	6	6	18	11.5
Comment		Recurrent cancer				Neoadjuvant chemotherapy	Neoadjuvant chemotherapy

ALND indicates axillary lymph node dissection; B/L, bilateral; CT, computed tomography; DVT, deep venous thrombosis; IV, intravenous; Lat, latissimus; MRM, modified radical mastectomy; PE, pulmonary embolism; SLNB, sentinel lymph node biopsy; TRAM, transverse rectus abdominis myocutaneous flap; VTE, venous thromboembolism.

in all patients who underwent breast surgery, but this difference did not reach statistical significance ($P = 0.15$).

Patients with VTE were evenly distributed between stage I, II, and III breast cancer, with 2 patients in each stage. One patient who developed a DVT had only ductal carcinoma in situ on the final pathology review. Patients diagnosed with VTE were initially treated with either continuous intravenous infusion of unfractionated heparin or LMWH (enoxaparin or dalteparin). All patients except for 1 (patient 2) were switched to oral warfarin for long-term treatment. The median duration of anticoagulation therapy was 11 months (range, 4–18 months). At the time of this report, patient 3 remains on warfarin 11 months after diagnosis of DVT. None of the other 6 patients has had a recurrence of VTE. No patient died as a consequence of VTE.

DISCUSSION

VTE is a potentially life-threatening complication in patients undergoing cancer surgery. The incidence of VTE and guidelines for VTE prophylaxis in patients undergoing surgery for breast cancer are not well established. Determining the incidence of VTE and defining patients at risk will aid in establishing recommendations for VTE prophylaxis.

We have developed clinical pathways for patients undergoing surgery for breast cancer to provide standard treatment guidelines that can be followed by clinicians and surgeons. These pathways include early ambulation and the use of elastic compression stockings and intermittent pneumatic compression devices during surgery and the early postoperative period. In the current study, we wished to determine the incidence of VTE in patients treated on these clinical pathways. The overall incidence of VTE within 60 days after surgery was 0.16% per procedure. This incidence is lower than that previously reported in the literature. In 1994, Clahsen et al,[11] as part of the European Organization for Research and Treatment of Cancer (EORTC) adjuvant breast cancer therapy trial 10854, reported a 0.8% rate of VTE within 6 weeks after surgery in breast cancer patients. In this trial, 2624 women with early breast cancer were randomly assigned to surgery alone or surgery followed by 1 course of chemotherapy. A total of 1332 women underwent surgery alone; of these, 6 developed superficial thrombophlebitis and 4 developed a DVT. No cases of PE were reported. If the patients with superficial thrombophlebitis are excluded, the true VTE rate is 0.3% per patient. Clahsen et al[11] reported

increased VTE rates in women undergoing mastectomies and in postmenopausal women, 2.3% and 2.0%, respectively. We observed a trend toward a higher incidence of VTE in patients undergoing longer and more complex surgeries, although this did not reach statistical significance.

There are several potential explanations for the lower VTE rate in our study. Our study was retrospective and hence limited to the data recorded in the different databases searched. Moreover, patients were assessed for VTE only if they presented with symptoms of VTE. It is estimated that only 40% of all patients with VTE develop clinical signs of the disorder.[12] It is possible that some patients treated during the study period developed only subclinical VTE and hence were not included in the incidence reported here. Inadequate follow-up data may also have resulted in underestimation of the true incidence. In our study, we had at least 60 days of follow-up data for over 95% of patients.

Another potential reason for the lower VTE incidence in our study is the use of clinical pathways, including early ambulation and mechanical DVT preventive devices. The effect of a systematic approach to VTE prophylaxis has not previously been reported in patients undergoing surgery for breast cancer. In the EORTC 10854 trial, VTE prophylaxis was left up to the individual treating physicians. Patients who received perioperative prophylactic subcutaneous heparin did experience a lower VTE rate than patients who did not (0.6% versus 2.0%). However, the VTE rate for patients who underwent surgery without perioperative chemotherapy and who received heparin was, unfortunately, not reported. Moreover, the use of other methods of VTE prophylaxis, such as antiembolism elastic stockings and intermittent pneumatic compression devices, was not reported. The authors commented on the longer hospital stay in patients with mastectomy, but the median length of stay was not specified and the use of early postoperative ambulation was not discussed.

In our study, as in previous studies,[11,13,14] increasing stage of breast cancer did not correlate with a higher rate of VTE. However, we recognize that the number of events in our study is too small to adequately establish whether the stage of breast cancer has a true impact on the rate of postoperative VTE.

The best modality for VTE prophylaxis in cancer patients undergoing surgery remains controversial. The overall incidences of DVT and fatal PE are estimated at 20% to 40% and 1%, respectively, in patients who do not receive perioperative thromboprophylaxis. The routine use of perioperative thromboprophylaxis with low-dose unfractionated heparin (5000 units subcutaneously every 8–12 hours) has been shown to reduce the incidence of DVT to 8% and the risk of a fatal PE to 0.01%.[9] LMWHs have been shown to produce a similar risk reduction. However, administration of heparins for thromboprophylaxis increases the risk of postoperative hematoma formation and bleeding. In breast cancer patients, administration of LMWH in the perioperative period has increased the risk of bruising and hematoma formation by 2- to 3-fold, with 11% to 18% of patients developing hematomas, as compared with approximately 7% of patients treated with elastic compression stockings.[15,16] Many surgeons prefer to use elastic compression stockings, intermittent pneumatic compression devices, or both for thromboprophylaxis, since these have not been shown to increase the risk of hemorrhagic complications and since the thromboprophylactic effects have been shown to be equivalent to those of low-dose heparins.[9,17–19] Our findings regarding the use of calf-length intermittent pneumatic compression devices and knee-length elastic compression stockings and the low incidence of VTE concur with these previous findings.

All the patients in our study who developed VTE received prolonged anticoagulation treatment (at least 4 months) without evidence of recurrence of VTE. Because of the small number of patients with VTE in our study, it is not possible to give specific treatment recommendations for VTE. The optimal duration of anticoagulation treatment in patients who develop VTE after breast cancer surgery is not well established. It is recommended that treatment proceed as long as the cancer is "active" and while the patient is receiving antitumor therapy.[7] In a recent study by Lee et al[20] of 606 patients with cancer, LMWHs were found to be more effective than an oral anticoagulant in reducing the risk of recurrent VTE. Only 17% of the patients in this study presented with breast cancer, and more than 66% of the patients in the study had metastatic disease. Whether prolonged anticoagulation treatment with LMWH is superior to oral anticoagulants in preventing VTE recurrence in breast cancer patients with postoperative VTE is not established.

CONCLUSION

The incidence of postoperative VTE in breast cancer patients treated on clinical pathways emphasizing early postoperative ambulation and the intraoperative and postoperative use of elastic compression stockings and intermittent pneumatic compression devices was very low. On the basis of these results, we do not recommend systemic DVT or PE prophylaxis in these patients treated with this standardized approach.

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