Venous Thromboembolic Disease in Autogenous Breast Reconstruction

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Abstract: Venous thromboembolic disease (VTE) is a cause of significant morbidity and mortality in patients with cancer. Large studies have estimated that VTE occurs in up to 1.1% of patients undergoing breast cancer tumor extirpation and in up to 1.5% of patients undergoing breast cancer reconstruction. This study sought to retrospectively review the experience of a large university practice with TRAM, DIEP, and latissimus flap reconstruction for mastectomy defects and evaluate our rate of VTE. In our series of 271 consecutive patients, 2 had deep venous thromboses, 2 had both deep venous thromboses and pulmonary emboli, and 2 had pulmonary embolus alone. VTE incidence was 2.2%, a relatively high rate compared with previously published, large population studies of VTE in breast reconstruction patients. Review of the literature suggests that physicians have poor compliance with established guidelines for prophylaxis and treatment of VTE in general and orthopedic surgery populations. Unfortunately, no specific guidelines are available for patients undergoing operative intervention for breast cancer or autogenous tissue based reconstruction. VTE is significantly under-diagnosed: clinical findings alone are unreliable, and the true prevalence may be greater than twice what is reported. Further research is needed in this largely unexplored field to determine appropriate means of VTE prophylaxis and treatment in the breast cancer population.

Key Words: venous thromboembolic disease, deep venous thrombosis, pulmonary embolism, breast cancer, autogenous tissue reconstruction

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Venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), pose significant threats to all hospitalized patients, both medical and surgical. Those considered at increased risk of VTE include trauma patients (particularly victims of spinal cord injuries), as well as patients in the critical care setting.[1] Women receiving breast reconstruction following mastectomy have additional, well-recognized risk factors for development of VTE, including age over 40, known diagnosis of cancer, previous VTE, central catheter placement, estrogen use, and undergoing surgical procedures.[1] Inherent differences in tumor characteristics and in the invasiveness of surgery for extirpation make literature from general surgery patients difficult to generalize to the breast cancer population. Retrospective studies have shown that patients with newly diagnosed metastatic breast cancer have a 2.8% incidence of VTE at 1 year, compared with 20% in patients with metastatic pancreatic cancer.[2] Previous studies of breast reconstruction have reported widely varying rates of DVT and PE associated with these procedures.[3–13] Thus, the incidence of VTE in this patient population remains uncertain.

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Venous thromboembolic events result in significant morbidity and mortality. The majority of PE deaths occur within hours of the embolic phenomenon, often secondary to unrecognized DVT. Morbidity from VTE includes postthrombotic syndrome and pulmonary hypertension with progression to right heart failure.[14] The financial costs of VTE are also significant. In cancer patients, initial hospitalization costs for diagnosis and treatment of VTE have been estimated at $20,065.[15]

Guidelines for prophylaxis and treatment of VTE in patients undergoing operations for abdominal and pelvic cancer are well established and are regularly revised.[1,16] However, there have been no published guidelines to date for prevention of VTE in patients receiving mastectomy reconstruction. A consensus panel has previously published clinical guidelines for DVT prophylaxis in plastic surgery patients,[17] and others have published generalized recommendations.[18,19] Cancer is known to produce a hypercoagulable state, placing cancer patients undergoing breast reconstruction at higher risk of VTE than other surgical candidates.[20] Data on appropriate VTE prophylaxis is lacking in the breast cancer population and is nearly absent for breast cancer reconstruction patients.

The current study sought to evaluate the incidence of venous thromboembolic disease in patients undergoing autogenous tissue breast reconstruction at a large university hospital. We also present a review of the available literature on this topic and make recommendations for further research assessing VTE incidence and prevention in this patient population.

PATIENTS AND METHODS

Records for all breast cancer patients undergoing mastectomy reconstruction using transverse rectus abdominis musculocutaneous (TRAM), deep inferior epigastric perforator (DIEP), or latissimus dorsi flaps at the University of Michigan between January of 1998 and August of 2007 were reviewed.

Approval from the University of Michigan Institutional Review Board (IRB# HUM 00012676) was obtained. All patients receiving TRAM, DIEP, or latissimus reconstruction performed by 3 attending surgeons between January 1, 1998 and August 31, 2007 were identified. Data were extracted from the University of Michigan's electronic medical record system and from hard copy medical charts. Data collected including patient age, height, weight, type of procedure (pedicled latissimus, pedicled TRAM, free TRAM, or DIEP flaps), timing of reconstruction (immediate or delayed), and operative time. Medical record review was used to identify preoperative and postoperative VTE prophylaxis, when given. Episodes of venous thromboembolic disease, including deep venous thrombosis and pulmonary embolism, were documented up to 90 days postoperatively.

Diagnosis of DVT was made with lower extremity duplex ultrasound, known to have 96% sensitivity and 98% specificity for diagnosis of DVT.[21] A negative ultrasound study is known to effectively eliminate the presence of clinically significant DVT.[22] Pulmonary embolism was identified using pulmonary embolism protocol computed tomography. This study is the recognized first line examination for patients with suspected pulmonary embolus and has high negative predictive value, meaning that a negative study

effectively rules out clinically significant PE.[23] Computed tomography is known to have high sensitivity (100%) and specificity (89%) for detection of PE.[24] Data were entered into a standard spreadsheet program (Microsoft Excel) and descriptive statistics were generated.

RESULTS

Review of the University of Michigan database yielded 271 breast cancer patients who had undergone autogenous tissue transfer for postmastectomy reconstruction. The majority of these patients (72.0%) underwent pedicled TRAM flaps. Patients receiving latissimus flap reconstruction comprised 20.3% of the cohort. Tissue expanders were placed at time of initial operation in 77.7% of latissimus flap patients. Immediate reconstruction was performed in 52.8% of the women. Seventy of the patients (25.8%) underwent bilateral reconstruction. Median operative time for all patients was 385 minutes. Median BMI in our series was 25.3. Patient demographic information is listed in Table 1.

All patients had sequential compression devices applied before induction of anesthesia and continued for the remainder of the hospitalization. Preoperatively, 4.4% of patients received VTE prophylaxis with unfractionated heparin or low molecular weight heparin, and 11.8% were administered postoperative pharmacologic prophylaxis. With the exception of 1 patient with a previous history of DVT, only patients operated on after mid-2006 (N = 32) received pharmacologic prophylaxis. This reflects a change in our practice based on a growing body of literature supportive of pharmacologic prophylaxis.

TABLE 1. Patient Demographics

No. patients	271
No. flaps	341
Age (yr)	
Median	47
Range	27–66
BMI	
Median	25.3
Immediate pedicled TRAM	
Bilateral	44
Unilateral	72
Immediate free TRAM	
Bilateral	2
Unilateral	7
Immediate pedicled latissimus	
Unilateral	18
Delayed pedicled TRAM	
Bilateral	22
Unilateral	57
Delayed free TRAM	
Unilateral	11
Delayed DIEP	
Unilateral	1
Delayed pedicled latissimus	
Bilateral	2
Unilateral	35
OR time (minutes)	
Median	385
Range	139–726

TABLE 2. Comparison Demographics for Patients With and Without VTE

	Patients With VTE	Patients Without VTE
No. patients	6	265
Age (yr)		
Mean	53.5	46.5
Median	47	47
Range	41–60	22–66
BMI		
Mean	27.4	25.8
Median	29.0	25.0
Range	18.7–31.2	15.7–41.6
Operative time (min)		
Mean	348	388
Median	350	385
Range	257–437	139–726
Pharmacologic prophylaxis		
Pre- and postoperative	0	12
Postoperative only	3	17
None	3	236

In this series, 6 episodes of VTE occurred, for an overall incidence of 2.2%. Comparison data between patients with and without VTE are listed in Table 2. Two patients had isolated DVT, 2 had DVT and PE, and 2 had PE alone. Diagnoses of PE were made with PE protocol CT scans. Diagnoses of DVT were made using duplex lower extremity ultrasound. Four events occurred in patients undergoing immediate pedicled TRAM flap, 1 in a delayed pedicled TRAM flap, and 1 in a delayed latissimus flap with tissue expander. Five patients with VTE had unilateral reconstruction and 1 had bilateral reconstruction. Three patients were treated with long term coumadin therapy, 1 with coumadin and inferior vena cava (IVC) filter placement, 1 with LMWH and IVC filter placement, and 1 with IVC filter placement alone.

One patient in the study had a prior DVT and received postoperative pharmacologic prophylaxis without VTE occurrence. One patient was known preoperatively to have a Factor V Leiden mutation. She received pharmacologic prophylaxis and had a postoperative DVT. Hypercoagulable workup of 1 patient with postoperative DVT and PE made a new diagnosis of methylene-tetrahydro-folate reductase deficiency.

DISCUSSION

Cancer patients are known to have a higher risk of VTE compared with noncancer patients undergoing surgery of equal duration and severity. Cancer surgery doubles the risk of DVT and triples the risk of fatal PE.[20] Prospective observational studies of breast cancer patients demonstrate a 1% risk of VTE within the first 2 years after diagnosis. Venous thromboembolic events within the first 2 years after breast cancer diagnosis are associated with a significant increase in mortality[2] and are the second most common cause of death in breast cancer patients after cancer itself.[25] Patients with VTE and malignancy are significantly more likely to be readmitted with recurrent VTE and have a significantly greater risk of death when compared with those with malignancy or VTE alone.[26]

TABLE 3. Rates of VTE in Patients Undergoing Breast Cancer Surgery and Chest Wall Reconstruction

Year	Author	Surgery Type	N	Number DVT (Rate)	Number PE (Rate)	VTE Rate	Notes
2007	Spear et al[4]	Pedicle TRAM	200	1 (0.5%)	2 (1.0%)	1.5%	2/30 morbidly obese patients with PE
2006	Mehara et al[6]	Free flap after mastectomy	952	9 (0.95%)	0	0.95%	
2006	Andtabaka et al[36]	Breast cancer ± reconstruction	4416	3 (0.07%)	4 (0.09%)	0.16%	Noninvasive prophylaxis
2005	Olsson et al[7]	Delayed free TRAM	16	2 (12.5%)	1 (6.3%)	18.8%	
2005	Wang et al[8]	Pedicle TRAM	107	2 (1.9%)	1 (0.9%)	2.8%	2/18 morbidly obese patients in study with DVT
2005	Gabbay et al[9]	Pedicle midabdominal TRAM	18	0	0	0	All pts morbidly obese
2005	Spear et al[3]	Pedicle TRAM ± XRT	150	1 (0.7%)	1 (0.7%)	1.3%	
2005	Spear et al[4]	Pedicle TRAM	200	1 (0.5%)	2 (1.0%)	1.5%	Same cohort as Spear et al 2007
2004	Guerra et al[11]	Bilateral DIEP	140	1 (0.8%)	0	0.8%	
2004	Hamdi et al[10]	Bilateral perforator flaps	53	2 (3.8%)	0	3.8%	
2000	von Tempelhoff et al[39]	MRM vs. BCS	190	2 (1.1%)	0	1.1%	All patients rec'd prophylaxis
1994	Clahsen et al[40]	MRM vs. BCS	1332	10 (0.8%)	0	0.8%	
1991	Arnez et al[12]	Free TRAM	50	1 (2.0%)	1 (2.0%)	4.0%	
1991	Wedgwood et al[37]	MRM	108	3 (2.8%)	2 (2.2%)	4.6%	Noninvasive prophylaxis
1991	Saphner et al[41]	Breast cancer surgery	321	1 (0.3%)	0	0.3%	Unclear MRM vs. BCS
1989	Fisher et al[42]	MRM vs. BCS	1326	2 (0.2%)	0	0.2%	
1987	Hartrampf et al[13]	Pedicle, delayed TRAM	300	0	2 (0.67%)	0.67%	

VTE Prophylaxis: Clinical Guidelines and Recommendations

The American College of Chest Physicians publishes a regularly updated guide to VTE prophylaxis.[1] Patients over the age of 60 undergoing surgery or those between the ages of 40 to 60 with additional risk factors (prior VTE, cancer, or known hypercoagulability) are classified as high risk and are recommended to have prophylactic unfractionated heparin (UFH, given 3 times daily) or low molecular weight heparin (LMWH, administered daily). Surgical patients in the highest risk category include those with multiple risk factors, including age over 60, cancer, prior VTE, major trauma, or known hypercoaguable states. For these high-risk patients, prophylactic UFH or LMWH are recommended for a period of 28 days following surgery. The American Society for Clinical Oncologists (ASCO) recommends administration of UFH or LMWH perioperatively for patients undergoing operative intervention. The Society's guidelines maintain that use of mechanical methods of prophylaxis alone (such as compression hose or sequential compression devices) are insufficient for prevention of VTE.[16]

A consensus panel of plastic surgeons has previously recommended that all patients receive perioperative sequential compression devices and be assisted in early ambulation. Additional recommendations include consideration of preoperative and postoperative pharmacologic prophylaxis for any patient over age 40, undergoing an extensive procedure, with a history of hormone use or malignancy, or with personal or family history of VTE.[16] Knee flexion at 5 degrees is also advocated to maximize flow through the popliteal vein.[16,19] More recent reviews in the plastic surgery literature have recommended pharmacologic prophylaxis for operations over 4 hours, including extensive body contouring procedures, abdominoplasty, and TRAM flaps.[27,19] Others have advocated an algorithmic approach to VTE prophylaxis with utilization of standardized Risk Assessment Models (RAMs).[18]

ENOXACAN I, a randomized, double blinded prospective trial, compared 10-day courses of UFH with LMWH for VTE prophylaxis in elective operations with curative intent for abdominal and pelvic cancers.[28] With preoperative and postoperative dosing, no significant differences in VTE were demonstrated by venography. The 2 treatment groups also showed no significant differences in bleeding complications or mortality, demonstrating that UFH and LMWH were equally safe and effective. The ENOXACAN II study,[29] a prospective, randomized, double-blind, placebo controlled trial, demonstrated a significant reduction in VTE when abdominal and pelvic cancer patients received 28 versus 7 days of postoperative LMWH prophylaxis. There were no differences between groups in hemorrhagic complications. All patients had mandatory venography at 1 month. These findings have been confirmed by prospective, randomized trials in similar populations by others.[30,31] Up to 20% of VTE events in this patient population occurred after discharge from the hospital.[30,31] For general surgery patients, a meta-analysis of 33 randomized, controlled trials in which preoperative and postoperative pharmacologic VTE prophylaxis was given confirmed that bleeding complications requiring reoperation occurred in less than 1% of patients.[32]

Physician Adherence to Guidelines

Surveys of physicians have suggested that clinical practices frequently do not follow published guidelines. The American College of Chest Physicians guidelines for VTE prophylaxis[1] are published regularly. Retrospective studies of US hospitals' practices for VTE prophylaxis 1 year after guideline publication demonstrate that 25% to 50% of patients undergoing abdominal surgery received inadequate or no prophylaxis.[33] In a large survey of physicians involved in cancer care,[34] only 52% of providers routinely used VTE prophylaxis for cancer patients undergoing operations. For cases in which no surgery was planned, fewer than 5% of physicians recommend prophylaxis. Surveys of breast surgeons have shown that 4.6% use no prophylaxis, while 41% use only mechanical VTE prophylaxis due to the perceived risk of bleeding complications.[35] This misconception appears to exist among surgeons despite published studies demonstrating only marginal increases in bleeding risks for general surgery patients receiving preoperative and postoperative anticoagulant prophylaxis.[1,32]

VTE in Breast Cancer Patients

In 2006, Andtbacka et al performed a retrospective analysis of the MD Anderson experience with VTE in breast cancer patients

undergoing operative intervention.[36] Of the 3900 patients evaluated, 18% received immediate breast reconstruction. With their protocol of early ambulation, antiembolism stockings and sequential compression devices, a VTE rate of 0.18% was documented at 60 days. The VTE rate in patients undergoing mastectomy with or without sentinel lymph node biopsy was 0.16%, compared with 0.25% for those receiving immediate reconstruction. Smaller, single-surgeon experiences with modified radical mastectomy have demonstrated VTE rates up to 4.6% using antiembolism stockings alone as prophylaxis.[37]

A prospective cohort study of 425 women comparing LMWH versus TED stockings during breast conservation surgery or mastectomy for breast cancer showed no clinically overt VTE events in either group.[38] Prospective randomized studies of UFH and LMWH in patients undergoing breast conservation treatment or modified radical mastectomy without immediate reconstruction have shown DVT rates of 1.1% in both groups.[39] Published reports of VTE incidence in patients undergoing primary breast cancer surgery is between 0.16% and 4.6%.[36,37,39–42]

VTE in Breast Cancer Reconstruction

Previously reported rates of VTE in autogenous tissue breast reconstruction have varied widely. Several smaller studies have noted relatively high rates compared with the 2.2% incidence observed in the current analysis. Arnez et al have documented VTE rates of up to 4.0% in a small published series of pedicled TRAM flaps.[12] A recent study of bilateral breast reconstruction with DIEP and SGAP flaps in 53 consecutive patients (33 of whom had breast cancer) documented an incidence of 3.8% for DVT with no pulmonary emboli reported.[10] Wang et al published a series of 107 consecutive patients undergoing pedicled TRAM reconstruction and found an overall VTE incidence of 2.8%, although a smaller cohort of 18 morbidly obese patients included in the study had a seemingly disproportionate number of events (2 of 18).[8]

Studies with patient numbers comparable with the current series have noted VTE rates somewhat lower than our 2.2%. Hartrampf's 1987 report on 335 pedicled TRAM flaps documented 3 pulmonary emboli (0.9%) and no deep venous thromboses.[13] A series of 952 consecutive mastectomy patients reconstructed with both immediate and delayed free flaps reported a VTE rate of 0.9%.[6] Other large studies of patients undergoing immediate and delayed DIEP flaps have demonstrated DVT rates of 0.8%.[11]

Our review of the literature found only 3 reports of large cohort studies of breast reconstruction with VTE incidences greater than 1.0%. Interestingly, all 3 reports appear to draw from the same patient population. Spear et al have reported VTE rates of 1.3% to 1.5% in their breast reconstruction patients.[3–5] Given the relative rarity of VTE, our study is underpowered to conclusively demonstrate the incidence of this disorder. However, it is notable that at 2.2%, our cohort demonstrates the highest rate of VTE in a large population of breast reconstruction patients reported to date. In summary, reports of VTE incidence in breast reconstruction patients vary widely, making the true rate of postoperative VTE in this patient population uncertain. A large, multicenter study with objective diagnostic criteria is required to determine the true incidence of VTE in this patient population. A summary of studies evaluating VTE in breast cancer surgery and chest wall reconstruction is provided in Table 3.

Validity of Current VTE Assessments

Despite the importance of early treatment for DVT and PE, clinical diagnosis of VTE is often delayed and likely underestimates its prevalence. A recent review of the MASTER registry, a multicenter registry of patients with VTE, has shown that a large proportion of patients with VTE received a delayed diagnosis.[43] Detection of acute DVT occurred in 47% of patients between symptom onset and 5 days, and in 27% of patients after at least 10 days of symptoms. Diagnosis of pulmonary embolus was more timely, occurring in 64% of patients between symptom onset and 5 days, and in 16% of patients after at least 10 days of symptoms. Significantly faster diagnosis of VTE occurred if multiple signs or symptoms of VTE were present and in patients with personal history of VTE. Detection of DVT was not hastened if other risk factors, including cancer, known thrombophilia, or recent surgery, were present. These data are particularly concerning given that a large, prospective cohort study has demonstrated 25% mortality within 7 days of an incident VTE event.[44] Other studies have documented an overall case fatality rate of 5% for DVT and 23% for PE; patients over 40 years of age with VTE have a greater than 10% mortality rate.[45] Early diagnosis is critical. The mortality rate of anticoagulated DVT patients is 0.4%, compared with a rate of 1.5% in anticoagulated PE patients.[46]

In a study by Elliott et al, outpatients with DVT presented for medical evaluation an average of 4.4 days after symptom onset, with 21% of patients presenting after 7 days. Five percent of outpatient DVT cases presented at least 21 days after symptom onset. After presentation, a diagnosis of DVT was typically made within 1 day; 80% of the delay in DVT diagnosis was attributed to failure to seek treatment. Diagnosis of pulmonary embolism was limited by failure to seek medical attention (a mean of 3 days), and by delays from presentation to diagnosis (a mean of 2 days). Among patients with PE, 17% were diagnosed at least 7 days and 5% at least 21 days after initial symptom onset. In this study, 92% of DVT diagnoses were made with a single study (compression ultrasound study), whereas over 60% of patients required more than 1 diagnostic test to confirm the diagnosis of PE. This latter finding may account for the longer time period from presentation to diagnosis.[14]

Clinical diagnosis of VTE is known to be unreliable. Classic signs and symptoms of DVT include swelling (88%), pain (56%), and tenderness (55%). For pulmonary embolism, symptoms include dyspnea (77%), tachypnea (70%), and chest pain (55%).[45] Presenting complaints of VTE may be nonspecific, and patients with concerning symptoms are accurately diagnosed by physical examination less than 50% of the time.[45] Homans sign (calf pain elicited by extreme dorsi-flexion) has been observed in only 8% of DVT cases. Homan himself denied the accuracy of this physical finding for detecting DVT.[47] Autopsy studies have demonstrated that only 30% of pulmonary emboli are correctly diagnosed prior to death. In a study comparing postsurgical versus medical patients, analysis showed a significantly higher percentage (64%) of postoperative patients with PE were diagnosed correctly prior to death.[48] Sadly, many VTE events remain undiagnosed until noted at autopsy.

Prospective studies have shown that clinical diagnosis of DVT[47,49] and PE[48] are unreliable. Data from large multicenter studies indicate that 92% of patients with a discharge diagnosis of DVT manifested at least 1 clinical sign on presentation.[45] Considered together, these data suggest that the incidence of DVT is likely grossly underestimated. In fact, some authors estimate that the true incidence of clinically significant VTE is 2.3 times greater than the rate currently reported based on clinical findings.[45]

CONCLUSION

Patients undergoing autogenous breast reconstruction after mastectomy have multiple risk factors for development of venous thromboembolic disease. This retrospective analysis of 271 consecutive patients demonstrated that 2.2% had a clinically diagnosed and objectively confirmed VTE. However, as events are rare and clinical diagnosis is known to underestimate true incidence, it is unlikely that this study is reflective of the actual incidence of VTE in this population. Further research is needed to clarify the true incidence of this potentially fatal problem and to identify appropriate VTE

prophylaxis in patients undergoing surgery for breast cancer tumor extirpation and breast reconstruction.

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