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Evaluation of an Extended-duration Chemoprophylaxis Regimen for Venous Thromboembolism after Microsurgical Breast Reconstruction

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Background : Patients undergoing free flap breast reconstruction are at a high risk for venous thromboembolism based upon Caprini scores. Guidelines for venous thromboembolism prophylaxis recommend high-risk groups receive extended chemoprophylaxis for several weeks after gynecological, orthopedic, and surgical oncology cases. Extended prophylaxis has not been studied in free flap breast reconstruction. The purpose of this study was to compare outcomes of free flap breast reconstruction patients who received extended venous thromboembolism (VTE) prophylaxis with those who received standard inpatient-only prophylaxis.
Methods : Patients undergoing microsurgical breast reconstruction were divided into two groups: standard VTE prophylaxis (Group I) and extended prophylaxis (Group II). Both groups received prophylactic subcutaneous heparin or enoxaparin preoperatively and enoxaparin 40 mg daily postoperatively while inpatient. Group II was discharged with a home regimen of enoxaparin 40 mg daily for an additional 14 days.
Results : In total, 103 patients met inclusion criteria (36 patients in Group I, 67 patients in Group II). The incidence of VTE was 1.5% in Group II compared with 2.8% in Group I (P = 0.6). There was no difference in reoperative hematoma between Group I (n = 0) and Group II (n = 1) (P = 0.7). Total flap loss was 2.2%.
Conclusions : Although this retrospective pilot study did not show statistical significance in VTE between those receiving extended home chemoprophylaxis (1.5% incidence) compared with inpatient-only chemoprophylaxis (2.8%), the risk of bleeding complications was similar. These results indicate that a larger, higher powered study is justified to assess if an extended home chemoprophylaxis protocol should be standard of care post free flap breast reconstruction. *(Plast Reconstr Surg Glob Open 2021;9:e3741; doi: 10.1097/GOX.0000000000003741; Published online 6 August 2021.)*

INTRODUCTION

Venous thromboembolism (VTE) causes mortality in 100,000 patients annually in the United States.[1] VTE is among the few life-threatening complications that can affect plastic surgery patients. Individualized risk stratification has been recommended for VTE prevention by the American College of Chest Physicians (ACCP) guidelines and is widely accepted among surgical disciplines.[2] The Caprini risk assessment model is a validated tool for calculating VTE risk and guiding prophylaxis strategy.[3–6] The ACCP initially published VTE prevention guidelines in 2005 and updated recommendations in 2012 for orthopedic, nonorthopedic, and nonsurgical patients.[2,7,8] The 2012 ACCP guidelines addressed plastic surgery patients.[2] Recommendations were limited by the paucity of level I evidence in plastic surgery. Although the 2012 ACCP guidelines recommended that individuals with a high VTE risk (Caprini score ≥5) undergoing abdominal or pelvic surgery for cancer should receive extended-duration pharmacologic chemoprophylaxis, postmastectomy microsurgical breast free reconstruction was excluded from this recommendation.[2] Data from the Venous Thromboembolism Prevention Study, a consortium of five centers, were used to extrapolate VTE risk for plastic surgery patients based upon Caprini scores.[4] However, the Venous Thromboembolism Prevention Study did not report on

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chemoprophylaxis beyond inpatient hospitalization. For Caprini scores higher than 8, the American Association of Plastic Surgeons recommends chemoprophylaxis.[9]

Current recommendations for VTE chemoprophylaxis in the plastic surgery literature following microsurgical breast reconstruction are not uniform. Prophylactic anticoagulation typically started 6–8 hours postprocedure and continued through the inpatient hospital duration.[5,6,10] The Caprini model stratifies the vast majority of patients undergoing microsurgical breast reconstruction as "high-risk."[5,11,12] Patients who undergo microsurgical breast reconstruction have at least a 3.4% incidence of a deep vein thrombosis (DVT).[13] Factors that contribute to high VTE incidence for microsurgical breast reconstruction include cancer status, elevated body mass index (BMI), prolonged operative times, decreased mobility, extended length of inpatient stay, and increased intra-abdominal compartment pressure.[13–15] The purpose of this study was to assess extended home regimen VTE chemoprophylaxis to standard, inpatient-only chemoprophylaxis after microsurgical breast reconstruction.

METHODS

Study Population

Following approval from the institutional review board at Indiana University, patients undergoing microsurgical breast reconstruction from 2013 to 2016 at our institution were retrospectively evaluated. Individuals who had breast reconstruction with an abdominally-based free flap (deep inferior epigastric artery perforator (DIEP), superficial inferior epigastric artery, and muscle-sparing transverse rectus abdominis myocutaneous) were included. Patients with breast reconstruction from alternative donor sites (eg, profunda artery perforator, transverse upper gracili, and superior gluteal artery perforator) were excluded. All patients received mechanical compression devices placed preoperatively and during the inpatient stay.[6,16] Group I was categorized as "standard regimen" and received 5000 units of subcutaneous heparin or 40 mg of subcutaneous enoxaparin preoperatively followed by 40 mg of enoxaparin (first dose given 12 hours postoperatively) daily while inpatient until discharge.[17] Group II was designated "extended prophylaxis" and was administered preoperative chemoprophylaxis (5000 units of subcutaneous heparin or 40 mg of subcutaneous enoxaparin) and daily enoxaparin 40 mg (first dose given 12 hours postoperatively) while inpatient, followed by 2 weeks of enoxaparin 40 mg daily after discharge. Patients in both groups received 325 mg daily of aspirin postoperatively continuing until 30 days after discharge. During the study period, a postoperative protocol management change was adopted to use extended chemoprophylaxis for all patients undergoing microsurgical breast reconstruction. Group I was comprised of consecutive patients from the beginning of the study, and group II patients were subsequently after the practice change.

Outcome variables were VTE, reoperative hematoma, surgical site infection, seroma, and flap loss in the postoperative period. Records were monitored for VTE occurrence for 4 months postoperatively or until the patient's next surgery after free flap reconstruction. Predictive variables were age, sex, BMI, hospital length of stay, Caprini score, and comorbidities (diabetes, smoking). VTE risk was assessed using the 2005 Caprini model for VTE which stratified patients into "very low" (0 points), "low" (1–2 points), "moderate" (3–4 points), and "high" (≥5 points) risk categories based upon ACCP guidelines.[2,11]

Statistical Analysis

Data are presented as means and percentages. Chi-squared and Fischer exact test were used to analyze dichotomous dependent variables (VTE, reoperative hematoma, surgical site infection, seroma, flap loss) and comorbidities as appropriate given the low number of events. Independent samples *t*-tests were used to analyze continuous variables (hospital length of stay, BMI, age). Data were managed using the IU REDCAP data capture tool and analyzed with SPSS version 24.0 (IBM Corp., Armonk, N.Y.).

RESULTS

There were 103 patients (180 flaps) who met inclusion criteria: 36 patients in Group I (standard inpatient prophylaxis) and 67 patients in Group II (extended chemoprophylaxis). One hundred patients underwent DIEP flap reconstruction, one patient underwent muscle-sparing transverse rectus abdominis myocutaneous flap reconstruction, and two patients underwent superficial inferior epigastric artery flap reconstruction. The average age was 49.4 (± 9.8) years for Group I and 48.7 (± 9.2) years for Group II ($P = 0.7$). Mean BMI in Group I was 31.7 (± 6.0) kg/m^2 compared with 30.7 (± 6.4) kg/m^2 in Group II ($P = 0.4$). There were eight smokers in Group I and 15 smokers in Group II ($P = 0.99$) (Table 1). Group I had six diabetics, and Group II had eight diabetics ($P = 0.6$). Seventy-seven patients (75%) underwent bilateral reconstruction, with the majority of those patients belonging to the extended regimen group ($P = 0.02$): 22 bilateral (61%), 14 unilateral (39%) in Group I and 55 bilateral (82%), and 12 unilateral (18%) in Group II. Average length of stay was 5.6 (± 1.3) days in Group I and 5.6 (± 2.4) days in Group II ($P = 0.8$). Mean Caprini score was 6.6 (±.7) in Group I and 6.6 (±.9) in Group II ($P = 0.9$). One patient in each group developed VTE (2.8% in Group I, 1.5% in Group II) ($P = 0.6$). One patient (Group II) experienced postoperative surgical hematoma, requiring takeback to the operating room ($P = 0.7$). Four patients (11.1%) in Group I developed surgical site infections, compared with 15 (22.4%) patients in Group II ($P = 0.2$). There were 14 seromas among the 103 patients (16.2% Group I, 11.9% Group II, $P = 0.6$). Group I flap loss was 3.4% (two flaps) compared with Group II (1.6%, two flaps) for a total flap loss rate of 2.2%. The average operative time was 528 ± 117 minutes.

The two patients who experienced VTE both had a prior history of VTE. The patient from Group I presented

Table 1. Risk Factors and Outcomes for Patients Undergoing Abdominal Free Flap Breast Reconstruction in the Standard Chemoprophylaxis and Extended Chemoprophylaxis Groups

Predictive Variables	Standard Chemoprophylaxis (Group I)	Extended Chemoprophylaxis (Group II)	*P*
Smoking, n (%)	8 (22.2%)	15 (22.4%)	0.99
Age, y (mean)	49.4 ± 9.8	48.7 ± 9.2	0.73
BMI, kg/m^2 (mean)	31.7 ± 6.0	30.7 ± 6.4	0.40
Caprini score (mean)	6.6 ± 0.7	6.6 ± 0.9	0.88
Length of stay, d (mean)	5.6 ± 1.3	5.6 ± 2.4	0.84
VTE, n (%)	1 (2.8%)	1 (1.5%)	0.58
Hematoma	0	1 (1.5%)	0.65
Flap loss, n (%)	2 (5.6%)	2 (2.3%)	0.61

with distal external iliac DVT on postoperative day 19 confirmed by venous duplex ultrasound. Computed tomography scan of her chest showed right upper and right lower lobe pulmonary emboli (PE). After evaluation by the hematology-oncology service, she was treated with bivalirudin, a direct thrombin inhibitor, received an inferior vena cava filter, and underwent a workup for heparin-induced thrombocytopenia, which was found to be positive. The patient was a 58-year-old woman with a BMI of 24.7. Her comorbidities included a recent history of smoking. She had undergone a bilateral mastectomy with immediate DIEP flap reconstruction with a total operating time of 704 minutes. Group II had one patient who experienced VTE. This patient presented with calf pain on postoperative day 22. A venous duplex ultrasound was ordered, which showed distal popliteal vein DVT. There was no PE. The patient was treated with 80 mg of enoxaparin twice daily for 2 weeks followed by 20 mg of rivaroxaban daily and eventually placed on 5 mg of apixaban twice daily. The apixaban was stopped 17 months after her presentation for DVT, and aspirin was started indefinitely. The patient was a 54-year-old woman with a BMI of 27.6. She did not have any significant medical problems. She had undergone a bilateral mastectomy with immediate DIEP flap breast reconstruction with a total operating time of 620 minutes.

DISCUSSION

DVT and PE are complications that can cause severe morbidity and mortality. Other surgical disciplines have evolved to institute more aggressive, extended prophylactic measures to prevent VTE for high-risk patients based on Caprini assessment. There are limited data on extended chemoprophylaxis in high-risk plastic surgery patients. We present a pilot series on an extended home regimen of chemoprophylaxis (enoxaparin 40 mg subcutaneously daily) for 2 weeks post discharge for patients undergoing microsurgical breast reconstruction. These patients otherwise received a similar treatment to the standard group (preoperative chemoprophylaxis before induction, enoxaparin 40 mg daily while inpatient, and 325 mg daily oral aspirin for 30 days). We did not find a higher rate of complications such as hematoma. Patients who received enoxaparin for an extended duration in our study had a 1.5% risk of VTE compared with 2.8% for patients who received standard, inpatient-only enoxaparin. Although this difference did not reach statistical significance, our study's 1.5% risk is lower than the historical more than 3% rate that has been found in other studies for breast reconstruction patients only receiving prophylaxis while in-house.[11,13] A recent retrospective review reported a VTE rate among microsurgical breast reconstruction patients as 1.3%, similar to our findings. However, specific chemoprophylaxis regimens were not assessed.[18]

One concern cited for the use of chemoprophylaxis in microsurgical reconstruction is increased postoperative hematoma risk, given the large volume of dissection, and potential for flap compromise from pedicle tamponade by a hematoma.[10,19] However, several studies have demonstrated clinical benefit with VTE prophylaxis without an increase in hematoma incidence.[3,10] Similarly, our study did not show a significant difference in reoperative hematoma rate or other complications with the extended enoxaparin regimen.

Chemoprophylaxis has been studied in body contouring, which also carries a high VTE risk.[20–23] In a previous study, body contouring patients designated as "high-risk" were given 7 days total of chemoprophylaxis. There were no patients with DVT.[22] Other investigators found a DVT incidence under 1% after administering enoxaparin for 7 days to 253 patients following abdominoplasty.[20] Patients in our study, postdischarge, received an additional 2 weeks of daily enoxaparin 40 mg subcutaneously for prophylaxis. The risk of VTE remains elevated after discharge, for up to 12 weeks following surgery.[24,25] Extended-duration chemoprophylaxis (up to 35 days) is used in high-risk patients (eg, abdominal/pelvic cancer operations, knee replacements) in other surgical disciplines such as orthopedic surgery, gynecology, general surgery, and urology, with level 1 evidence support.[26–30] When extended VTE prophylaxis is administered in other surgical disciplines, it is most commonly given for 28 days.[2,31,32] A randomized double-blinded study showed decreased VTE risk for patients undergoing abdominal/pelvic cancer operations if daily enoxaparin 40 mg was administered for 27–31 days compared with 6–10 days.[27] Patients undergoing abdominal free flap breast reconstruction may possibly benefit from a longer duration of chemoprophylaxis. However, patient compliance with chemoprophylaxis may decrease as the duration increases. A study analyzing over 1200 patients with hip fractures found only one in five patients were compliant with 28 days of chemoprophylaxis.[33] In addition, patients in our investigation received enoxaparin 40 mg daily subcutaneously. This dosing may be inadequate for some patients based upon antifactor Xa levels.[34] Enoxaparin 30 mg twice daily may be more optimal dosing, but compliance is likely to decrease by doubling the frequency of administration of the subcutaneous injection. Therefore, the duration of our extended regimen (14 days) and daily dosing (enoxaparin 40 mg) may not be optimal for VTE prevention. A larger study duration is necessary to determine antifactor Xa levels. However, prolonging the treatment and increasing the frequency will likely hinder compliance.

Several limitations exist in our study. The patients were retrospectively reviewed. A clinical practice change of a more aggressive home prophylaxis regimen was initiated after a VTE event approximately a year and a half into the collection period rather than prospective randomization. Our limited sample size (total n = 103 patients) did not allow for multivariate regression modeling as VTE was rare. Therefore, confounders are not controlled. A power calculation ($\beta = 0.2$, $\alpha = 0.05$) demonstrates that nearly 2000 patients would be required in each group for 80% power to achieve statistical significance in VTE prevention based on our event rates. Additionally, a screening duplex to evaluate all patients during a specified time frame was not performed. Our results may indicate that the risk reduction in VTE with extended chemoprophylaxis may be clinically irrelevant or underpowered. However, given the morbidity and mortality of a DVT or PE, a larger study would be justified.

CONCLUSIONS

Patients undergoing an abdominal free flap for breast cancer reconstruction have an increased risk for VTE often because of the length of the operation, elevated BMI, cancer history, and age. Our chemoprophylactic protocol is 5000 units of subcutaneous heparin or 40 mg of enoxaparin given preoperatively, enoxaparin 40 mg daily while inpatient, aspirin 325 mg daily for 30 days, and enoxaparin 40 mg daily postdischarge for an additional 14 days for patients with a Caprini score of 5 or higher. Patients having prophylactic mastectomies, under age 40, and with a BMI less than 25 kg/m^2 may not meet criteria. Imaging is obtained to rule out DVT and PE based on clinical presentation. This pilot study showed that extended-duration chemoprophylaxis can be applied to these patients without an increase in bleeding complications or flap loss. There was no statistical significance between VTE in the extended chemoprophylaxis group (1.5% incidence) and the standard inpatient-only chemoprophylaxis group (2.8%). However, given the high morbidity and mortality of VTE, we continue to use the extended chemoprophylaxis regimen at our institution. Our findings with the small sample size indicate a larger, higher powered study is justified to assess if an extended home chemoprophylaxis protocol should be standard of care post free flap breast reconstruction.

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