Preoperative Screening Using Venous Duplex Scanning Does Not Alter the Outcome in Patients at High Risk of Postoperative Venous Thromboembolism

Takashi Yamaki*, Motohiro Nozaki, Hiroyuki Sakurai, Masaki Takeuchi, Kazutaka Soejima and Taro Kono

Department of Plastic and Reconstructive Surgery, Tokyo Women's Medical University, Tokyo, Japan

Abstract: *Purpose*: To assess whether preoperative screening using venous duplex scanning (VDS) of the bilateral lower extremities is useful for identifying patients at risk of developing postoperative venous thromboembolism (VTE).

Materials and Methods: Three hundred fifty-two consecutive referral patients at high or highest risk for postoperative VTE according to the guidelines of the American College of Chest Physicians were studied. After VDS, all patients received low-dose unfractionated heparin for postoperative thromboprophylaxis. Patients were then followed for 3 months after surgery for investigation of clinically significant VTE.

Results: Three hundred thirty patients were finally enrolled. Of these, orthopedic surgery patients were most common (140 patients, 42.4%), followed by general surgery (104 patients, 31.5%) and gynecologic (42 patients, 12.7%) surgery patients. Preoperative VDS identified 66 (20.0%) patients with deep vein thrombosis (DVT). Twenty-three (7.0%) patients had proximal DVT and the remaining 43 (13.0%) had distal DVT. Postoperative symptomatic VTE was found in 26 (7.9%) patients who had no evidence of preoperative DVT. Twenty-two patients developed calf DVT, two developed proximal DVT and two developed pulmonary embolism. In contrast, no propagation of DVT or new thrombus formation was found after surgery in patients who had preoperative DVT. Multivariate analysis showed that an age of >75 years (OR 2.57, 95% CI 1.14-5.82, $p = 0.023$) was the only significant predictor of postoperative VTE.

Conclusions: Preoperative screening does not identify patients at risk of developing clinically significant thromboembolic events.

Keywords: Deep vein thrombosis, venous thromboembolism, venous duplex scanning, preoperative screening.

INTRODUCTION

Accurate and immediate diagnosis of venous thromboembolism (VTE) still remains a difficult challenge for clinicians. Because of the increasing awareness of postoperative VTE, selection of patients who require adequate prophylaxis is of primary importance. Without prophylaxis, the incidence of hospital-acquired deep vein thrombosis (DVT) is approximately 10-40% among surgical patients and 40-60% following major orthopedic surgery [1-3].

According to the guidelines of the American College of Chest Physicians (ACCP), pharmacological thromboprophylaxis has been performed in most patients at high risk of postoperative VTE using injectable antithrombotics [1, 2]. Based on the results of numerous randomized clinical trials and meta-analyses, the routine use of both low-dose unfractionated heparin (LDUH) and low-molecular-weight heparin (LMWH) reduces the risk of both asymptomatic and symptomatic VTE resulting from general surgical procedures by at least 60%. Furthermore, extending thromboprophylaxis from 1 week to 4-6 weeks after surgery reduces the incidence of late episodes of symptomatic VTE [4, 5].

*Address correspondence to this author at the Department of Plastic and Reconstructive Surgery, Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan; Tel: +81-3-3353-8111; Fax: +81-3-3225-0940; E-mail: yamaki@prs.twmu.ac.jp, Yamakit@aol.com

While high-risk groups for VTE can be identified, it is not possible to predict which individual patients in a given risk category will develop a clinically important thromboembolic event. Furthermore, massive pulmonary embolism (PE) usually occurs without warning, and there is often no opportunity to resuscitate patients who suffer this complication. Early detection of preoperative DVT may lead to a significant reduction in the incidence of postoperative VTE. Therefore, the present study was undertaken to assess whether preoperative screening using venous duplex scanning (VDS) of the bilateral lower extremities is useful for identifying patients at risk of developing postoperative venous thromboembolism (VTE) undergoing elective surgery.

MATERIALS AND METHODS

Patients

From March 2005 to December 2007, a total of 352 consecutive referral preoperative patients, who were at high or highest risk for postoperative VTE according to the ACCP guidelines [1, 2], were prospectively evaluated using VDS. The presence of leg symptoms at initial presentation, including swelling, pain, and erythema was recorded. The patients' risk factors for VTE, including active cancer, congestive heart disease, hormone replacement therapy, immobilization, inflammatory bowel disease, known thrombophilia, previous DVT, renal failure and stroke were all evaluated. The

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thrombophilia work-up conducted for this study included determination of protein C, protein S, antithrombin III, antiphospholipid antibody, homocysteine and plasminogen. Factor V Leiden and Prothrombin G20210A were excluded because all of the patients were Japanese.

After completion of the examinations, all patients received LDUH during admission. For higher-risk patients including those undergoing orthopedic, general, gynecologic, or urologic surgery, two to three administrations of LDUH (5,000 U tid) were performed, with the use of graduated compression stockings and/or intermittent pneumatic compression devices. Preoperative oral anticoagulation or antiplatelet therapy was not used in this study. In patients who were found to have preoperative DVT, intermittent pneumatic compression devices were not used. Exclusion criteria in this study included: (1) patients who were undergoing emergency surgery, (2) patients undergoing inferior vena cava filter insertion, (3) patients who had received thrombolytic therapy (including both systemic and catheter-directed infusion) and (4) features of chronic DVT on duplex scan results.

Venous Duplex Scanning

All VDS procedures were performed by one experienced physician (T.Y.). A color duplex scanner (LOGIQ 7 PRO; GE Yokogawa Medical Systems, Tokyo, Japan) with a 5-10-MHz transducer was used. Initially, each patient was placed supine in the reverse Trendelenburg position at 15°. Examination began at the distal segment of the external iliac vein and the common femoral vein, and moved to the femoral vein at the adductor canal. The deep femoral, the anterior and posterior tibial veins were also recorded. Afterwards, the patient was placed prone with the knee flexed at 30°, and the residual popliteal, peroneal, gastrocnemius and soleal veins were evaluated [6]. The diagnosis of DVT was based on both noncompressibility of the vein on B-mode, and lack of spontaneous flow on color Doppler imaging. If there was no intraluminal defect with full venous compressibility and a normal flow, the examination result was considered negative. Thrombosis was considered to be proximal if it involved the deep veins in the pelvis, the thigh, and popliteal region with or without calf vein thrombosis. Thrombosis was considered as distal if it involved only the calf veins. VDS was performed at the time of referral and at postoperative days 7, 30, and 90.

Study Outcome

The primary study outcome was the incidence of confirmed symptomatic VTE, defined DVT, non-fatal PE, or both, at 3 months. Development of non-fatal PE was defined as a perfusion/ventilation mismatch on lung scan and/or an intraluminal filling defect on spiral CT of the chest in patients with suspected PE symptoms including dyspnea, chest pain and syncope. VDS of the lower extremities was performed at each visit, and a new or recurrent DVT was defined as a new non-compressible segment of the vein on B-mode, and lack of spontaneous flow on color Doppler imaging.

Statistical Analysis

All data were analyzed using StatView for Windows (Version 5.0, SAS Institute Inc., Cary, NC, USA). Wilcoxon's nonparametric rank sum test was used to evaluate differences between means for continuous data, and chi-squared test was used to evaluate differences between proportions. To evaluate which risk factors were independent predictors of symptomatic recurrent VTE, potential confounding variables were chosen using univariate analysis ($p < 0.10$), and final odds ratio (OR) and 95% confidence interval (CI) were calculated using multiple logistic regression analysis. Continuous data were expressed as mean ± standard deviation (SD). Statistical significance was defined as $p < 0.05$.

RESULTS

Patients

Table **1** shows the baseline characteristics of the study patients. Of the 352 consecutive patients evaluated, 22 were

Table 1. Baseline Characteristics of the Study Patients

Preoperative Variables	Data
Characteristics	
Number of patients eligible	330
Mean age (y)	64.8 ± 14.8
Female gender (%)	245 (74.2)
Leg symptoms	89 (27.0)
Number of patients with preoperative DVT (%)	66 (20.0)
Primary Care Department (%)	
Orthopedic surgery	140 (42.4)
General surgery	104 (31.5)
Gynecologic surgery	42 (12.7)
Neurosurgery	17 (5.2)
Major trauma	6 (1.8)
Urology	4 (1.2)
Others	17 (5.2)
Risk Factors (%)	
Active cancer	94 (28.5)
Congestive heart failure	10 (3.0)
Hormone replacement therapy	28 (8.5)
Immobilization	50 (15.2)
Inflammatory bowel disease	4 (1.2)
Known thrombophilia	12 (3.6)
Protein C deficiency	0 (0)
Protein S deficiency	3 (0.9)
Antithrombin III deficiency	4 (1.2)
Positive antiphospholipid syndrome	3 (0.9)
Hyperhomocysteinemia	0 (0)
Abnormal plasminogen	2 (0.6)
Previous history of DVT	40 (12.1)
Pregnancy	17 (5.2)
Renal failure	15 (4.5)
Stroke	7 (2.1)
Varicose veins	29 (8.8)

excluded on the basis of the criteria described previously. Thus, 330 patients were eligible for this study. The mean age of the patients was 64.8 (range 25-90) years and 245 (74.2%) were female. Among the 330 referrals, orthopedic surgery patients were the most common (140 patients, 42.4%), followed by general surgery (104 patients, 31.5%) and gynecologic (42 patients, 12.7%) surgery patients. In this study, an active cancer was the most common risk factor for DVT (94 patients, 28.5%), followed by immobilization (50 patients, 15.2%), previous history of DVT (40 patients, 12.1%), varicose veins (29 patients, 8.8%), hormone replacement therapy (28 patients, 8.5%), pregnancy (17 patients, 5.2%), renal failure (15 patients, 4.5%), and known thrombophilia (12 patients, 3.6%). Of the 330 referral patients, 66 (20.0%) were found to have DVT before surgery.

Evaluation of Initial DVT

Table **2** shows the distribution of DVT at initial examination. Twenty-three patients (7.0%) had proximal DVT, and the remaining 43 (13.0%) had distal DVT, the latter proportion being significantly higher (p = 0.010). There were 34 (10.3%) patients with isolated venous segment DVT, and the remaining 32 (9.7%) had multisegment DVT. In the isolated venous segment, distal veins had a significantly higher proportion of DVT compared to proximal veins (p <0.0001). On the contrary, a significantly higher proportion of proximal DVTs were found in patients with multisegment DVT (p = 0.070).

Table 2. Distribution of DVTs Detected by VDS in Patients Undergoing Elective Surgery

Distribution of Preoperative DVT	No. of Segments (%)	*p*-Value
Proximal DVT	23 (7.0)	
Distal DVT	43 (13.0)	0.010
Total	66 (20.0)	
Isolated Segment	**No. of Segments (%)**	
Proximal DVT	2 (0.6)	
Distal DVT	32 (9.7)	< 0.0001
Total	34 (10.3)	
Multisegment		
Proximal DVT	21 (6.4)	
Distal DVT	11 (3.3)	0.070
Total	32 (9.7)	

Clinical Events

Postoperative VTE was found in 26 (7.9%) patients (Table **3**). There were no significant differences in gender distribution or preoperative leg symptoms between patients with postoperative VTE and those without. On the other hand, mean age was significantly higher in patients who had postoperative VTE (p = 0.0002). Postoperative symptomatic VTE was found in patients who did not have any evidence of DVT preoperatively. Interestingly, no propagation of DVT or new thrombus formation was found after surgery using serial VDS among the 66 patients who had preoperative DVT.

Table 3. Characteristics of Patients With and Without Postoperative VTE

Variables	Postoperative VTE n=26	No Postoperative VTE n=304	*p*-Value
Age (y)	72.4 ± 10.7	63.9 ± 15.4	0.0002
Female gender (%)	22 (84.6)	223 (73.4)	0.208
Preoperative leg symptoms (%)	3 (11.5)	86 (28.3)	0.065
Preoperative DVT (%)	0 (0)	66 (21.7)	0.008
Duration of pharmacological thromboprophylaxis (days)	18.4 ± 7.4	16.9 ± 13.7	0.320

Because the Japanese Ministry of Health, Labor and Welfare currently does not approve the use of LMWH for postoperative thromboprophylaxis, LDUH was the most frequently used antithrombotic in this study. The mean duration of thromboprophylactic drug administration was 18.4 days in patients who had postoperative VTE and 16.9 days in patients with no postoperative VTE, and there was no significant difference in the duration of pharmacological thromboprophylaxis (p = 0.320).

During 3 months of follow-up, 22 patients developed distal DVT, 2 developed proximal DVT and the remaining 2 developed pulmonary embolism. Among the 26 patients, postoperative VTE was found in 18 (69.2%) on day 7. Fifteen patients developed distal DVT, one developed proximal DVT, and two developed PE. At day 30, 6 patients had distal and 1 had proximal DVT. Only one patient developed symptomatic calf DVT during the rehabilitation phase at day 90 (Table **4**). Among 26 patients with postoperative VTE, 22 (84.6%) had orthopedic, 2 had neurosurgical, 1 had general and 1 had gynecologic surgery. In 22 patients who had orthopedic surgery, 20 had total knee replacement surgery.

Table 4. Summary of Postoperative VTE

Events	Day 7	Day 30	Day 90	Total
Symptomatic VTE	18	7	1	26
DVT	16	7	1	24
Proximal DVT	1	1		2
Distal DVT	15	6	1	22
PE	2			2

Risk Factors for Postoperative VTE

The initial risk factors were tested by univariate analysis (Table **5**), and five potential risk factors were selected. Of these, an age of >75 years (OR 2.57, 95% CI 1.14-5.82, p=0.023) was finally found to be the only significant risk factor of postoperative VTE using multivariate analysis.

Table 5. Univariate Analysis of Potential Risk Factors for Postoperative VTE

Risk Factors	All Patients n=330	Postoperative VTE n=26	*p*-Value
Age, yr			
> 75	91	15	0.026
≤ 75	239	11	
Gender			
Female	245	22	0.032
Male	85	4	
Leg symptoms			
Yes	89	3	0.046
No	241	23	
Active cancer			
Yes	94	6	0.516
No	236	20	
Congestive heart failure			
Yes	10	1	0.807
No	320	25	
Hormone replacement therapy			
Yes	28	2	0.878
No	302	24	
Immobilization			
Yes	50	2	0.232
No	280	24	
Inflammatory bowel disease			
Yes	4	0	0.416
No	326	26	
Known thrombophilia			
Yes	12	0	0.157
No	318	26	
Previous history of DVT			
Yes	40	2	0.474
No	290	24	
Pregnancy			
Yes	17	0	0.904
No	313	26	
Renal failure			
Yes	15	1	0.798
No	315	25	
Stroke			
Yes	7	0	0.281
No	323	26	
Varicose veins			
Yes	29	1	0.282
No	301	25	

DISCUSSION

The most validated approach for patients with suspected DVT is contrast venography, which was previously regarded as the “gold standard” for detecting the presence and distribution of DVT. Recently, however, noninvasive VDS has largely replaced contrast venography as the initial diagnostic test for DVT, and has high sensitivity and specificity [6]. At the same time, the accuracy of VDS varies among both operators and medical centers [7]. While VDS has lower sensitivity for detecting DVT in asymptomatic patients, its accuracy appears to be improving, and as a result, an increasing number of clinical trials of thromboprophylaxis have been utilizing ultrasound outcomes.

Table 6. Final Multivariate Analysis of Potential Risk Factors for Postoperative VTE

	Adjusted Odds Ratio (95% CI)	*p*-Value
Age >75 years	2.57 (1.14-5.80)	0.023
Female gender	2.94 (0.99-8.77)	0.052
Leg symptoms	0.33 (0.10-1.13)	0.078

While most asymptomatic DVTs are not clinically relevant, there is strong concordance between the "surrogate" outcome of asymptomatic DVT and clinically significant VTE [4, 8, 9]. In patients with lower extremity ischemia undergoing arteriography or revascularization, preoperative DVT may be present. Libertiny *et al*. detected DVT by VDS in 20% of 136 patients with peripheral vascular disease prior to arteriography or surgery [10]. In contrast, Passman *et al*. reported low rates of preoperative asymptomatic DVT (4%) and postoperative asymptomatic DVT (3%) in patients undergoing infrainguinal arterial reconstruction, although 25% of the patients received anticoagulation therapy postoperatively [11]. Because of the ongoing risk of VTE in trauma patients, several investigators have recommended that high-risk patients undergo screening for asymptomatic DVT using VDS [12, 13]. One limitation to this approach, however, is the rather low sensitivity of VDS for detecting asymptomatic DVT [14]. Furthermore, screening using VDS may not prevent PE [14]. Explanations include migration of the peripheral thrombus to the lung before VDS can be obtained, a PE origin other than the proximal lower extremities, or the inability of VDS to detect 100% of thrombi present [15].

Most prophylaxis trials of subcutaneous LDUH have involved administration of 5,000 U 1 to 2 h before surgery, followed by administration of 5,000 U bid or tid until patients are either ambulatory or are discharged from hospital [1, 2, 16, 17]. One meta-analysis of randomized studies among orthopedic surgery patients comparing prophylactic LMWH with fixed low-dose or adjusted-dose unfractionated heparin reported an incidence of venous thrombosis of 15.9% in a group given LMWH and 21.7% in heparin groups ($p = 0.01$), with a lower incidence of proximal venous thrombosis in the LMWH group (5.4% *vs* 12.5%; $p < 0.0001$) [18]. In another study comparing LMWH and LDUH in patients undergoing knee arthroplasty, the incidence of postoperative VTE was not significant [19]. It may be assumed that LDUHs are being used in most Japanese patients because the Japanese Ministry of Health, Labor and Welfare currently does not approve LMWH for postopera-

tive thromboprophylaxis. This might explain the utility of preoperative screening, because patients receiving LDUH have a significantly higher incidence of postoperative VTE than those receiving LMWH. However, the apparent lack of VDS positivity before surgery in our postoperative patients was a cause for concern. Among 26 patients with postoperative thromboembolic events, none had DVTs before surgery. Most studies that employ routine screening for DVT may underestimate the true rate of symptomatic VTE because early screening for, and treatment of, asymptomatic DVT virtually eliminates the potential for these thrombi to progress and become symptomatic [4, 8, 9], assuming that preoperative surveillance is of no use for identifying patients at risk of VTE receiving pharmacological thromboprophylaxis.

Aside from postoperative VTE, the risk of post-thrombotic syndrome could support the use of surveillance VDS. Our previous study showed that the presence of high peak reflux velocity in the proximal deep veins 2 years after initial proximal DVT is a strong predictor of advanced symptoms of post-thrombotic syndrome at 6-year follow-up point [20]. Early detection of proximal DVT might be useful for selecting patients who require much longer follow-up.

Controversies still exist regarding the relationship of preoperative coagulation test to subsequent postoperative VTE. Ginsberg *et al*. [21] tested the preoperative level of plasma thrombin-antithrombin III (TAT) in patients undergoing major hip or knee surgery. They found that TAT level was significantly higher in patients who developed DVT than in those who did not (p=0.035), and concluded that preoperative TAT level well correlate with the risk of developing DVT after major orthopedic surgery. On the contrary, Iversen *et al*. [22] reported that preoperative TAT and soluble fibrin in patients undergoing colorectal disease did not predict postoperative DVT. Further studies are needed to determine the prophylaxis and screening of DVT can be made based on the results of preoperative coagulation test.

While the incidence of postoperative VTE is decreased by pharmacological thromboprophylaxis, the risk factors for VTE are also changing. In the FOTO Study, an age of at least 75 years and an absence of ambulation before hospital discharge were the only significant (p <0.05) predictors of symptomatic VTE at 3 months: a body mass index of >30 kg m^{-2}, a previous history of DVT, varicose veins, type of surgery, and general anesthesia were poor predictors for postoperative VTE [23]. Our study also demonstrated that an age of >75 years (OR 2.57, 95% CI 1.14-5.82, p = 0.023) was the only significant predictor of postoperative VTE.

Our study had some potential limitations. First, we failed to identify patients who would benefit most from preoperative surveillance VDS. Finding a DVT at initial examination was found to have no significant impact on the risk of recurrent VTE events within 3 months. This was most likely because of the recent advances in pharmacological thromboprophylaxis rather than the performance of surveillance VDS. This is in agreement with a recent epidemiological study indicating that a high number of patients benefit from extended-duration thromboprophylaxis [24]. Nevertheless, both patients with and without postoperative VTE did not differ significantly with respect to the duration of pharmacological thromboprophylaxis. Second, our study had a limited sample size with rather few clinical events, which may indicate a potential for type II statistical error. A large sample size is required to confirm the relationship between symptomatic and objectively proven DVT or PE, and asymptomatic proximal DVT detected before surgery and clinically important VTE outcome.

In conclusion, the prevalence of postoperative VTE was 7.9% among patients at high or highest risk for VTE, and these VTEs occurred in patients with no evidence of preoperative DVT. Presence of preoperative DVT identified by VDS is not predictive of postoperative propagation of DVT or new VTE formation. Multivariate analysis showed that an age of >75 years was the only significant predictor of postoperative VTE. These results suggest that preoperative screening does not identify patients at risk of developing clinically significant thromboembolic events.

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