Deep Vein Thrombosis Risk Stratification

Pulmonary Thromboembolism and Antithrombotic Therapy

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SUMMARY

Pulmonary thromboembolism (PTE) is a life-threatening disease which always presents in patients with deep vein thrombosis (DVT). There are few statements in guidelines regarding indications for anticoagulation based on the location of DVT. We investigated whether the relative risk of PTE depends on thrombus location and bleeding complications with anticoagulation therapy. Between January 1 and July 10, 2007, 461 patients underwent lower extremity venous ultrasound studies, and 129 patients were diagnosed as DVT (60 males, 66.9 ± 13.3 years). We retrospectively studied the incidence of PTE and bleeding complications associated with anticoagulation therapy. Average follow-up period was 536 ± 324 days. Above and below knee thrombosis was present in 60 and 69 patients, respectively. Warfarin was administered in 60 patients. Nine patients developed PTE. Multivariate analysis showed the absence of anticoagulation therapy and location of DVT (above knee) to be significantly correlated with onset of PTE (anticoagulation; $P < 0.01$, location; $P = 0.02$). However, the incidence of bleeding was not significantly different between above knee and below knee vein thrombosis ($P = 0.72$). In conclusion, below knee vein thrombosis carries a relatively low risk of PTE, but the incidence of bleeding complications does not depend on thrombosis location. This suggests that the indication of anticoagulation therapy should be based on DVT location. (Int Heart J 2013; 54: 166-170)

Key words: Pulmonary thromboembolism, Anticoagulation therapy, Below knee vein thrombosis

Pulmonary thromboembolism (PTE) is a fatal disease which causes pulmonary artery occlusion and severe respiratory disorder. Approximately 80 to 90% of embolism cases are due to a thrombus which is formed in intrapelvic or lower limb veins. Some studies have reported that massive PTE associated with an unstable hemodynamic state has 58.3% mortality in the early phase, and even when stable, has 15.1% mortality.¹⁾

Patients are at high-risk of thrombus formation in the perioperative period, during prolonged bed rest, or if malignancy is present, in addition to those exhibiting the classic Virchow triad. The fact that 90% of PTE originate from lower limb veins highlights the significance of early detection and treatment of deep vein thrombosis (DVT). It has become easier to identify DVT, with the growth in the importance of lower limb venous ultrasound.

Many ongoing DVT guidelines such as the ACCP and JCS guidelines recommend anticoagulation therapy with unfractionated/low molecular heparin or warfarin for DVT in the absence of contraindications. In cases when DVT is identified, the 8th ACCP guideline recommends anticoagulation therapy with short-term intravenous or subcutaneous heparin injection (indicated as grade IA). The JCS guidelines also recommend anticoagulation therapy (as class I/IIa).^{2,3)} However, some studies suggest that the risk of PTE is comparatively low in below knee DVT.⁴⁾ There is still controversy regarding uniform appli-

cation of anticoagulation therapy to DVT. Moreover, unnecessary anticoagulation therapy should be avoided because it sometimes causes severe bleeding complications. The current study examined the relationship between PTE risk, location of DVT, and bleeding complications in anticoagulation therapy.

METHODS

Study design and populations: Between January 1 and July 10, 2007, we performed 461 lower limb venous ultrasound studies and 129 patients were diagnosed as DVT. We retrospectively examined the incidence of PTE and bleeding complications in these patients. The follow-up period was from January 1, 2007 to September 15, 2009. The patient characteristics examined were sex, age, comorbidities, perioperative period, prolonged bed rest, DVT/PTE history, warfarin use, C-reactive protein (CRP), and PTE. We defined the perioperative period as the term within 3 months after a surgery, and prolonged bed rest as more than 48 hours of immobility in the preceding month.⁵⁾ We defined above knee thrombosis as inferior vena cava, common/external iliac, femoral, popliteal, or saphenous great vein thrombosis and below knee thrombosis as anterior/posterior tibial, peroneal, or soleal vein thrombosis. We classified thrombus existing both above and below knee veins as above knee thrombosis. For lower limb venous ultra-

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sound studies, we used an Aplio80, AplioXV, or Aplio VG (Toshiba) and a 7.5 MHz (linear type) probe.

Study outcome and statistics: To diagnose PTE, we performed ventilation perfusion scintigraphy and contrast enhanced computed tomography at the time of onset of any symptoms that suggested PTE, such as dyspnea, chest pain, and tachypnea. A bleeding complication was defined as anemia that required blood transfusion, or 2.0 g/dL decrease of hemoglobin. To evaluate bleeding risk, we used the HAS-BLED score.⁶⁾ This score is defined based upon the existence of various factors; hypertension (uncontrolled, >160 mmHg systolic), abnormal renal/liver function, stroke (previous history, particularly lacunar), bleeding history or predisposition, labile international normalized ratio (INR) including warfarin use, elderly (> 65 years), and drugs/alcohol (antiplatelet agents, nonsteroidal anti-inflammatory drugs) (Table I). Data were tested for significance with Fisher's exact test, Mann-Whitney *U* test, independent *t*-test, and multiple logistic regression analysis as appropriate using SPSS (SPSS Chicago, IL).

Table I. Clinical Features and Points of HAS-BLED Score

Letter	Clinical characteristic	Points
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1~2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1~2

INR indicates international normalized ratio.

RESULTS

Baseline characteristics: Of 129 patients, 60 were male. Mean age was 66.9 ± 13.3 . The average follow-up period was 536 ± 324 days. A total of 212 vessels were diagnosed as DVT. The location was the inferior vena cava in 1, iliac vein in 7, femoral vein in 43, popliteal vein in 31, saphenous great vein in 5, tibial vein in 9, peroneal vein in 13, and soleal vein in 103. Co-existing conditions were 45 (34.9%) malignancy, 13 (10.0%) collagen vascular diseases, 12 (9.3%) trauma/fracture, 23 (17.8%) diabetes mellitus, 6 (4.7%) cerebral infarction, 18 (14.0%) perioperative period, and 20 (15.5%) prolonged bed rest. There were 24 (18.6%) patients with a past history of DVT/PTE. Above and below knee vein thrombosis was present in 60 and 69 patients, respectively. There were no significant differences between these two groups with regard to comorbidities, D-dimer, and CRP, but there were differences for age, perioperative period, prolonged bed rest, DVT/PTE history, and warfarin use (Table II).

Clinical outcome and multivariate analyses: Nine patients had developed clinical PTE (Table III), only 1 of which was below knee thrombosis. Univariate analysis of the incidence of PTE was performed using age, sex, malignancy, collagen vascular disease, trauma/fracture, diabetes mellitus, cerebral infarction, perioperative period, prolonged bed rest, past history of DVT/PTE, CRP, D-dimer, location of thrombus (above knee), and absence of warfarin use. We determined cut off values as the average for age, and as the median for CRP and D-dimer.

As a result, 4 factors were significantly correlated to PTE events: age ($P = 0.03$), past history of DVT/PTE ($P = 0.01$), location of thrombus (above knee) ($P = 0.01$), and absence of warfarin use ($P = 0.04$) (Table IV). Moreover, we performed multivariate analysis among these 4 factors in relation to PTE

Table II. Baseline Characteristics of the 129 Study Patients

	Total	Above knee (<i>n</i> = 60)	Below knee (<i>n</i> = 69)	<i>P</i>
Male/Female	60/69	31/29	29/40	0.29
Age (years)	66.9 ± 13.3	64.2 ± 14.6	69.4 ± 11.7	0.03*
Malignancy	45 (34.9%)	25 (41.7%)	20 (29.0%)	0.14
Collagen vascular disease	13 (10.0%)	5 (8.3%)	8 (11.6%)	0.57
Trauma/Fracture	12 (9.3%)	3 (5.0%)	9 (13.0%)	0.14
Diabetes mellitus	23 (17.8%)	10 (16.7%)	13 (18.8%)	0.82
Cerebral infarction	6 (4.7%)	1 (1.7%)	5 (7.2%)	0.22
Perioperative period	18 (14.0%)	3 (5.0%)	15 (21.7%)	0.01*
Prolonged bed rest	20 (15.5%)	4 (6.7%)	16 (23.2%)	0.01*
DVT/PTE history	24 (18.6%)	16 (26.7%)	8 (11.6%)	0.04*
Warfarin (+)	60 (46.5%)	35 (58.3%)	25 (36.2%)	0.01*
D-dimer ($\mu\text{g/mL}$)	11.6 ± 17.2	13.5 ± 23.3	10.2 ± 11.1	0.59
CRP (mg/dL)	2.7 ± 3.7	3.0 ± 4.1	2.5 ± 3.3	0.98
PTE	9 (7.0%)	8 (13.3%)	1 (1.4%)	0.01*
HAS-BLED score	2.36 ± 1.36	2.58 ± 1.15	2.17 ± 1.39	0.07
Bleeding complication	2 (1.6%)	1 (1.7%)	1 (1.4%)	0.72
Venous thrombosis vessels	212	111	101	
Inferior vena cava	1	1		
Iliac vein	7	7		
Femoral vein	43	43		
Popliteal vein	31	31		
Saphenous great vein	5	5		
Tibial vein	9	1	8	
Peroneal vein	13	2	11	
Soleal vein	103	21	82	

Continuous values are average $\pm$ SD. CRP indicates C-reactive protein; DVT, deep vein thrombosis; and PTE, pulmonary thromboembolism. * $P < 0.05$ (either Fisher's exact test, Chi-square test, or Mann-Whitney *U* test as appropriate).

Table III. Characteristics of Patients Who Developed PTE

	Age/sex	Warfarin	PT-INR	PTE/DVT history	Co-existing disease	AK/BK	DVT location
Case 1	47M	–	1.27	+	Hypertension	AK	Lt Femoral v Lt Popliteal v Lt Soleal v
Case 2	43F	–	0.91	–	Hyperlipidemia Pill medication	AK	Rt Popliteal v Rt Soleal v
Case 3	77F	–	0.99	–	Malignant lymphoma	AK	Bilateral Femoral v Bilateral Soleal v
Case 4	55M	–	0.93	–	Polyarteritis nodosa	AK	Rt Peroneal v Lt Femoral v Lt Popliteal v
Case 5	64F	–	1.10	–	Lung carcinoma Hyperlipidemia	AK	Lt Soleal v Rt Popliteal v Rt Peroneal v
Case 6	38M	–	1.02	+	Pulmonary hypertension	AK	Rt Soleal v Rt Popliteal v
Case 7	69F	–	0.99	+	Diabetes mellitus Gastric carcinoma Lumbar compression Fracture	AK	Rt Peroneal v Lt Femoral v Lt Popliteal v
Case 8	32M	+	1.99	+	Deficiency of Protein S	AK	Rt Femoral v Rt Popliteal v
Case 9	60F	–	0.97	+	Superficial thrombophlebitis	BK	Rt Soleal v

AK indicates above knee; BK, below knee; and v, vein.

Table IV. Univariate Analysis of PTE and Patient Factors

Parameter	P
Age (> 66.9)	0.03*
Sex (male)	NS
Malignancy	NS
Collagen vascular disease	NS
Trauma/Fracture	NS
Diabetes mellitus	NS
Cerebral infarction	NS
Perioperative period	NS
Prolonged bed rest	NS
DVT/PTE history	0.01*
CRP (> 0.8)	NS
D-dimer (> 5.9)	NS
Location (above knee)	0.01*
Warfarin (-)	0.04*

DVT indicates deep vein thrombosis; PTE, pulmonary thromboembolism; and NS, not significant. * $P < 0.05$ (chi-square or Fisher's exact test).

Table V. Multivariate Analysis of PTE and Patient Factors

Parameter	OR (95% CI)	P
Age (> 66.9)	0.21 (0.033-1.41)	0.11
DVT/PTE history (+)	7.23 (1.01-51.9)	0.049*
Location (above knee)	16.75 (1.65-169.6)	0.02*
Warfarin (-)	25.0 (2.31-250.0)	0.008*

OR indicates odds ratio; 95% CI, 95% confidence interval; DVT, deep vein thrombosis; and PTE, pulmonary thromboembolism. * $P < 0.05$ (multiple logistic regression analysis).

events. The results showed that a past history of DVT/PTE, location of thrombus (above knee), and absence of warfarin use were significantly correlated with PTE progression. In particular, a strong correlation was shown between thrombus location (above knee) ($P = 0.02$) and absence of warfarin use ($P = 0.008$) with PTE events (Table V). On the other hand, among the 129 patients, 2 patients who had used warfarin developed severe bleeding complications. Although both presented melena, we could not identify the exact bleeding location in one case (Table VI). There was no difference between the incidence of bleeding complications and thrombus location ($P = 0.72$). Moreover, there was no significant difference in the HAS-BLED score between these two groups ($P = 0.07$) (Table II). Finally, we performed subgroup analysis between PTE de-

velopment and warfarin use among those with below knee DVT. However, multivariate analysis could not be performed because of the small number of PTE events, and there was no significant difference in PTE development between those with and without warfarin (Table VII).

DISCUSSION

Many guidelines uniformly recommend anticoagulation therapy once DVT is diagnosed. The 8th ACCP guideline recommends long-term anticoagulation therapy because 15 to 50% of chronic DVT patients experience a recurrence, and this often progresses to PTE. This applies not only to proximal DVTs but also to distal veins including soleal veins. Douketis, *et al* reported that recurrence of DVT was a risk factor for fatal PTE.⁷⁾ On the other hand, anticoagulation using warfarin sometimes causes bleeding complications. Even though PT-INR may be within an appropriate range, the incidence of intracranial hemorrhage is 0.2% per year.⁸⁾ Some studies have reported total bleeding event rates of 0.32 to 2.1%, with the fa-

Table VI. Characteristics of Patients Who Developed Bleeding Complications

	Age/sex	Warfarin	PT-INR	Co-existing disease	AK/BK	DVT location	HAS-BLED	Bleeding location
Case 1	74F	+	1.21	Rt femoral neck fracture Rheumatoid arthritis Interstitial pneumonia	BK	Bilateral soleal v	1	Lower gastrointestinal tract (diverticulum)
Case 2	53F	+	1.93	Hypertension Chronic gastritis Chronic kidney disease (post-transplantation)	AK	Rt popliteal v Rt soleal v	3	Lower gastrointestinal tract (unidentified)

Table VII. Subgroup Analysis of PTE Development Among Those With Below Knee DVT

	PTE (+)	PTE (-)
Warfarin (-)	1	43
Warfarin (+)	0	25

$P = 0.64$ (Fisher's exact test).

tal bleeding event rate being 0 to 0.25% per year.⁹⁾ Wysowski, *et al* reported that warfarin was among the top 10 drugs having the largest number of serious adverse event reports in the FDA Adverse Event Reporting System.¹⁰⁾ The use of anticoagulation needs to be rigorously evaluated.

Below knee veins are especially important in the origination and progression of thrombosis. Popliteal/femoral venous thrombosis, which results in progression to PTE, was reported to originate from soleal veins.¹¹⁾ On the other hand, McDonald, *et al* reported that the rate of soleal venous thrombosis progression to popliteal veins was only 3% and indicated that anticoagulation for below knee venous thrombosis is comparatively unnecessary.¹²⁾ Although ongoing guidelines recommend anticoagulation for below knee vein thrombosis, this indication is still controversial.

The present study results indicate DVT/PTE history, thrombus location (above knee), and absence of warfarin use were significant factors. Though it seems natural that warfarin use is associated with prevention of PTE, it is interesting that thrombus location is a risk equivalent to the presence/absence of warfarin. Our study revealed that the risk of PTE is comparatively lower in below knee vein thrombosis than in above knee thrombosis. Moreover, 2 (1.6%) patients who took warfarin developed bleeding complications, and there appeared to be no association between bleeding and thrombus location. Age, past bleeding history, and chronic liver/kidney diseases are well known to be associated with bleeding risk with warfarin use. Recently, the HAS-BLED score has become a useful bleeding risk score among patients with atrial fibrillation.⁶⁾ In addition, an observational study revealed that the incidence of bleeding complications is higher in Japanese than in Caucasian populations.¹³⁾ The present study results show the incidence of PTE was comparatively lower in the below knee thrombosis group. However, the incidence of bleeding complications was not significantly different between the two groups, even after taking into consideration the multiple bleeding risks including warfarin use by using the HAS-BLED score. Moreover, subgroup analysis of the below knee thrombosis patients showed no significant difference in PTE incidence regardless of warfarin use. This implies the possibility that unnecessary anticoag-

ulation is undertaken in a proportion of DVT cases. It is preferable to develop new DVT guidelines which precisely predict the incidence of PTE according to DVT location, taking into account the high incidence of bleeding complications in the Japanese population. However, this does not mean anticoagulation is unnecessary for all cases of below knee DVT. In high risk patients, anticoagulation with adequate dose and duration would be necessary even in below knee DVT.

Limitations: Our study was a single-center retrospective study. Due to the small number of PTE/bleeding complication events, potential confounding factors may exist.

Conclusions: Although ongoing guidelines recommend anticoagulation therapy in all DVTs regardless of location, below knee vein thrombosis carries a comparatively low risk of PTE development. Considering bleeding complications, it may not always be necessary to apply anticoagulation therapy in all DVT patients. More randomized prospective trials based on thrombosis location are required.

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