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Short-Term Anticoagulant Therapy and Thrombus Location Are Independent Risk Factors for Delayed Recanalization of Deep Vein Thrombosis

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Background: Prompt recanalization of the vein containing the thrombus is an important goal during the initial treatment of DVT, and risk factors for delayed recanalization in patients with deep vein thrombosis (DVT) in the lower extremities need to be determined.





Material/Methods: A total of 174 patients with DVT in lower extremities were recruited from June 2014 to March 2015 at our hospital. Duplex ultrasound scanning was conducted for all patients at 1 and 6 months after baseline evaluation. We divided the patients into recanalization and non-recanalization groups and analyzed risk factors for delayed recanalization.

Results: The univariate analysis revealed that an oral anticoagulant time of less than 3 months and venous thrombus location were risk factors for delayed recanalization ($P < 0.01$). However, age, gender, hypertension, diabetes, pulmonary embolism, incidence factors, the use of catheter-directed thrombolytic (CDT) drugs, and inferior vena cava filter (IVCF) implantation had no influence on the incidence of delayed recanalization in patients with DVT ($P > 0.05$). The multivariate analysis showed that patients with an anticoagulant time of less than 3 months had a lower incidence of recanalization than those with an anticoagulant time of more than 3 months ($OR = 2.358$, $P < 0.05$). The risk of delayed recanalization in patients with proximal DVT was 7 times higher than that in patients with distal DVT.

Conclusions: Duration of anticoagulant treatment of less than 3 months and venous thrombus location are independent risk factors for delayed recanalization of DVT in the lower extremities.

MeSH Keywords: **Anticoagulants • Risk Factors • Venous Thrombosis**

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Background

Deep vein thrombosis (DVT) is a common cause of mortality and disability in the lower extremities and has a high incidence of morbidity due to post-thrombotic syndrome (PTS) [1–3]. Many studies have shown that delayed recanalization in patients with DVT is a predictive factor of PTS [4–6]. Complete recanalization within 3 months and no reflux is related to low or no risk of PTS [7]. Therefore, prompt recanalization of the vein containing the thrombus is an important goal in the clinical treatment of DVT. However, the recanalization rate of DVT is low. The cumulative complete recanalization rate is 38.8% during the first 6 months and 73.8% at 36 months following initial treatment [8]. Many factors are reported to have an effect on the delayed recanalization, such as age, DVT location (proximal or distal), and duration of treatment [9–13]. However, contrary results were suggested by different researchers for the same factors [9,10]. Moreover, nearly all these researches are based on warfarin as the long-term oral anticoagulant, which interacts with many commonly used medications and foods, and its activity has to be monitored by blood testing for the international normalized ratio (INR) to ensure that an adequate yet safe dose is taken. Thus, the analyzed results of risk factors for delayed recanalization might have been affected by warfarin itself in previous studies.

Furthermore, new oral anticoagulants may have an advantage in reducing the PTS and increasing the rate of recanalization compared with warfarin [14,15]. Rivaroxaban, one of the new oral anticoagulants, has better stability than warfarin. Using rivaroxaban as the long-term oral anticoagulant may achieve more pure and accurate results to help comprehensively understand the risk factors for delayed recanalization of DVT and improve early treatment strategies for DVT.

In this study, 174 patients taking rivaroxaban as the long-term oral anticoagulant with DVT were reviewed at our hospital from June 2014 to March 2015 to explore risk factors for delayed recanalization in patients with DVT of the lower extremity.

Material and Methods

Patient data

The data of all patients with lower extremity DVT from June 2014 to March 2015 were reviewed in this study. The inclusion criteria were as follows: (1) lower extremity DVT confirmed by duplex ultrasound scanning (DUS); (2) receipt of anticoagulation therapy; and (3) complete medical record during follow-up. The inclusion criteria of patients received catheter directed thrombolysis (CDT) were as follows: (1) patients with a symptomatic iliofemoral DVT; (2) symptoms for fewer than

14 days; (3) good functional status, life expectancy of 1 year or more; and (4) low risk of bleeding [16].

Criteria for determination of recanalization

Recanalization was determined by DUS. Complete occlusion (delayed recanalization) was defined as no Doppler blood signal in the vein. Partial occlusion was defined as a partially compressed venous segment with a normal or diminished Doppler blood signal. Patent (complete recanalization) was defined as resolution of the thrombus allowing for the vein to be completely compressed [17]. The number of patients in the recanalization group was the sum of patients with partial occlusion and patency DVT.

Grouping

According to the DUS results, patients were divided into recanalization and non-recanalization groups. Gender, age, venous thrombus location, incidence factors, hypertension, diabetes, accompanied pulmonary embolism, inferior vena cava filter (IVCF) implantation, anticoagulation regimen, and the use of CDT drugs were investigated.

Proximal and distal DVT

Distal thrombus was defined as thrombus only involving popliteal vein or (and) calf vein; Proximal thrombus was defined as the thrombus at least involving femoral vein and above and meanwhile, the thrombus may also involve the popliteal vein or (and) calf vein.

Anticoagulant treatment

All patients received oral rivaroxaban as the anticoagulation regimen. The dose was given as 10 mg twice daily for at least 3 weeks, followed by 10 mg once daily. The regimen was recommended to last for 6 months for all patients. At the same time, non-steroidal anti-inflammatory and antiplatelet medicines were not permitted. Some of the patients didn't finish the 6-month regimen for economic burden or non-compliance. Anticoagulant time, which the patients actually received, was considered as short term anticoagulant therapy if less than 3 months. Otherwise, the situation was considered as long-term.

Statistical analysis

All data were analyzed using the SPSS version 13.0 statistical package. The homogeneity of variance and normality of the data were tested using the Levene test and Kolmogorov-Smirnov test. Univariate analysis was performed using the chi-squared test or t-test. Binary logistic regression was used in the multivariate analysis to detect risk factors of delayed

Table 1. Univariate analysis of risk factors for delayed recanalization.

Characteristic	Non-recanalization (n=46)		Recanalization (n=128)		RR	χ^2	P
	N	(%)	N	(%)			
Gender							
Male	26	(56.5)	56	(43.8)	0.598	2.215	0.137
Female	20	(43.5)	72	(56.2)			
Short term treatment*	26	(56.5)	39	(30.5)	2.967	9.815	0.002
Primary hypertension	5	(10.9)	13	(10.2)	0.927	0.019	0.554
Diabetes	2	(4.3)	5	(3.9)	0.894	0.017	0.896
Incidence factors	36	(78.3)	89	(69.5)	0.634	1.275	0.259
PE	11	(23.9)	23	(18.0)	0.697	0.761	0.383
IVCF	8	(17.4)	17	(13.3)	0.727	0.465	0.495
CDT	3	(6.5)	10	(7.8)	0.823	0.082	0.775
Location of DVT					6.444	7.747	0.005
Proximal DVT	44	(95.7)	99	(77.3)			
Distal DVT	2	(4.3)	29	(22.7)			

PE – pulmonary embolism; IVCF – inferior vena cava filter; CDT – catheter-directed thrombolytic. * Short term treatment means anticoagulant time of less than 3 months.

recanalization for DVT. *P*-values <0.05 were considered statistically significant.

Results

General information

A total of 640 patients with DVT were reviewed for enrollment in this study between June 2014 and March 2015 at a single center; 174 patients met the inclusion criteria, including 82 males and 92 females with a mean age of 49.8±15.8 years (range: 16~82 years); 55 patients had history more than 14 days. Proximal and distal DVT were observed in 143 (both common and superficial femoral veins: n=37; common femoral vein: n=20; superficial femoral vein: n=32; iliac vein: n=15; iliac vein combining common and superficial femoral veins: n=19; both iliac vein and common femoral veins: n=13 and both iliac vein and superficial femoral veins: n=7) and 31 patients (both calf and popliteal veins: n=17; calf vein: n=6 and popliteal vein: n=8), respectively. Eighty-nine patients had obvious incidence factors (surgery: n= 55, long period of being bedridden: n=44, fracture: n=36, and cancer: n=8). Primary hypertension, diabetes, and pulmonary embolism were observed in 18, 7, and 34 patients, respectively. Sixty-five patients received anticoagulation therapy for less than 3 months (short-term anticoagulant therapy), 13 patients received CDT, and 17 patients underwent IVCF implantation at initial treatment.

The mean age of patients receiving CDT was 49.5 years (range of 24 to 82 years). The total urokinase dose was 5.15±0.23 million units. Of these patients, 6 patients experienced complete recanalization and 4 patients experienced partial recanalization;

46 patients had delayed recanalization, with a mean age of 49.7±15.9 years, and 128 patients had recanalization (73.6%), with a mean age of 49.9±16.0 years. The recanalization group included 56 males and 72 females.

Univariate analysis of risk factors for delayed recanalization in patients with DVT

The statistical analysis is shown in Table 1. There was a significant difference in the location of the DVT between the recanalization and delayed recanalization groups (*p*=0.005). Similarly, short-term anticoagulant therapy was related to delayed recanalization (*p*=0.002). However, the univariate analysis failed to reveal any influence of gender, age, primary hypertension, diabetes, pulmonary embolism, IVCF, CDT or incidence factors on the risk for delayed recanalization in patients with DVT (*p*>0.05).

Multivariate analysis of risk factors for delayed recanalization

According to the univariate analysis of delayed recanalization, 2 risk factors influenced the rate of recanalization of the

Table 2. Multivariate analysis of risk factors for delayed recanalization.

Characteristic	Wald	Odd Risk (OR)	P value	95% Confidence interval	
				Lower	Upper
Anticoagulation	4.644	2.358	0.031	1.080	5.103
Type of DVT	6.644	7.117	0.010	1.600	31.648

Table 3. State of veins assessed by DUS during the 6 months follow-up.

Venous segment	n	Vein state	1 month	6 months
Iliac vein	54	Patent (%)	13.8	20.7
		Partially occluded (%)	37.1	36.0
		Occluded (%)	49.1	43.3
Common femoral vein	89	Patent (%)	15.3	27.5
		Partially occluded (%)	43.6	36.6
		Occluded (%)	41.1	35.9
Superficial femoral vein	95	Patent (%)	26.2	37.8
		Partially occluded (%)	30.5	33.5
		Occluded (%)	43.3	28.7
Popliteal vein	142	Patent (%)	32.7	42.8
		Partially occluded (%)	38.4	38.9
		Occluded (%)	28.9	18.6
Calf vein	121	Patent (%)	38.6	57.1
		Partially occluded (%)	47.6	35.6
		Occluded (%)	12.8	7.3

vein containing the thrombus and were included in the multivariate analysis. Table 2 shows that location of DVT ($P=0.010$, $OR=2.358$) and short-term anticoagulant therapy ($P=0.031$, $OR=7.117$) were independent risk factors related to delayed recanalization in patients with DVT.

State of veins assessed by DUS during the 6-month follow-up

Table 3 shows the state of veins (patent, partially occluded, or occluded), as detected by DUS during the 6-month follow-up. Iliac vein, common femoral vein, superficial femoral vein, popliteal vein, and calf vein were affected in 54, 89, 95, 142, and 121 patients, respectively. The patency rates in all the segment veins had increased at 6 months. The rate of recanalization was higher in calf veins (92.7%) than any other venous segment at 6 months.

Discussion

In patients with deep vein thrombosis, recanalization is a long process. The causes of delayed recanalization within 6 months of initial treatment are very complicated. In our study, both the univariate and multivariate analyses revealed that the frequency of recanalization in patients with distal DVT was significantly higher than that in patients with proximal DVT. The rate of recanalization was lower in patients with short-term anticoagulant therapy. Therefore, we propose that short-term anticoagulant therapy and thrombus location are independent risk factors for delayed recanalization.

Short-term anticoagulant therapy as a risk factor for delayed recanalization

It is known that anticoagulation treatment cannot actually dissolve the thrombus, but rather prevents the development of

acute DVT. Moreover, anticoagulation therapy may also reduce the rate of relapse DVT and increase the incidence of recanalization [18]. However, inadequate or delayed anticoagulant therapy may result in the formation of post-thrombotic syndrome. Park et al. [19] reported that the recanalization rate of distal DVT is significantly different between patients with and without anticoagulation therapy (84% vs. 64.8%). However, the author did not analyze the influence of anticoagulation time on thrombus regression. The optimal duration of anticoagulation therapy for patients with DVT in the lower extremities is unclear [20]. In the present study, we found that recanalization in patients with an anticoagulant time of less than 3 months had a lower incidence of recanalization than those with an anticoagulant time of more than 3 months (60.0% vs. 81.7%). Moreover, only 27.6% of patients showed complete resolution of DVT at 6 months following the initial treatment. The frequency of partial or complete recanalization was lower than that reported by Prandoni [8], Ageno [21], and Asbeutah [11].

This may be because the patients in this study had poorer compliance in anticoagulant therapy. Poor compliance means that patients received anticoagulant treatment of less than 3 months prior to the diagnosis of DVT [22]. In our study, 37.4% of patients had poor compliance, and the recanalization rate was lower in those patients than in others with good compliance (60.0% vs. 81.7%). Another reason may be due to our relatively low dose of rivaroxaban. In our study, the dose of rivaroxaban was lower than the recommended dose for DVT treatment of 2×15 mg for 3 weeks and then 1×20 mg. A new Japanese study found that patients with acute DVT and/or PE had a similar efficacy and safety profile with rivaroxaban (2×10 mg for 3 weeks and then 1×15 mg for 12 months) and control treatment (anticoagulant with VKA), consistent with that of the worldwide EINSTEIN DVT and PE program [23]. This suggests that a lower dose of rivaroxaban may be practicable in Asian populations. Considering that high price prevents patients from receiving rivaroxaban, we tried to use a low dose of rivaroxaban in our study to increase compliance to anticoagulant therapy. Moreover, the low recanalization rate is also influenced by the interval from the onset of disease to the start of anticoagulant therapy; the 31.6% of patients with history of present illness more than 14 days may also contribute to the low recanalization rate in this study.

A meta-analysis pooled 11 studies of 3203 patients with residual thrombosis and indicated that the OR of relapse DVT was 2.02 (95%CI, 1.62–2.50) compared to patients without residual thrombosis [24]. Boutitie et al. [25] reported that patients who received anticoagulation treatment from 1 to 1.5 months had an increased risk of recurrence thrombus compared to patients receiving anticoagulant therapy for more than 3 months (OR=1.52). Similar result was achieved in our study, in which 21 patients experienced recurrence DVT. There was a significant difference with respect to recurrent DVT between the

recanalization and non-recanalization groups (7.8% vs. 23.9%). Thus, anticoagulant therapy should be extended beyond 3 months to reduce recurrence thrombus and improve the incidence of recanalization at initial treatment in patients with DVT.

Venous thrombus location as a risk factor for delayed recanalization

Proximal and distal DVTs are 2 types of DVTs. Isolated distal DVT is associated with transient risk factors, whereas proximal DVT is more associated with chronic risk factors [26]. Most researchers believe that recanalization of a vein containing a thrombus is quite difficult and time-consuming. Patients with proximal DVT have a higher incidence of recurrence and a lower recanalization rate compared to patients with distal DVT [7,27,28]. In addition, a 5-year follow-up study revealed that all patients with distal DVT experienced resolution, but recanalization was only observed in 85% of patients with proximal DVT at 6 months following the initial treatment [11]. In the present study, among patients with distal DVT, 29 (93.5%) experienced recanalization, while 69.2% of patients with proximal DVT experienced recanalization.

The recanalization rates were gradually elevated for the iliac vein, common femoral vein, superficial femoral vein, popliteal vein, and calf vein in our study. A reasonable hypothesis regarding recanalization rate is that as the location of thrombus becomes more distal, the thrombus resolves faster. Similar findings were reported by Park [19] and Brandao et al. [29]. In addition, Park et al. [19] reported that the rate of recanalization in the calf vein was as high as 82% during the first 3 months following initial treatment. This may be because the calf vein has a lower thrombosis load compared to the proximal vein. Moreover, the high incidence of recanalization in the calf vein may be attributed to the positive effect of the calf muscle pump on venous return [30].

Age, gender, primary hypertension, diabetes, and incidence factors

Piovella et al. [10] reported that recanalization rate decreases with age during a 12-month follow-up study. However, in the present study, there was no statistically significant difference in age and rate of recanalization. The univariate analysis showed that the recanalization rate was equal between males and females ($p=0.137$). Moreover, the study showed no statistically significant relationship between DVT recanalization rate and primary hypertension, diabetes. Similar findings were reported by Ageno et al. [21], who found that hypertension and obesity had no influence on recanalization in patients with DVT.

Our study also did not find a relationship between DVT recanalization rate and risk factors. Thrombophilia is a risk factor

of thrombosis, which has been reported in 18.8% to 46% of young patients with DVT and may increase risk of relapse DVT [12,31,32]. Genetic testing for FV R506Q, PT G20210A, and MTHFR C677T is recommended for patients after the first episode of unprovoked DVT, and the results may be beneficial to protect from recurrence [33]. In the present study, thrombophilia was not screened among these patients, which may be a defect in our study.

CDT, IVCF and PE have no influence on delayed recanalization in patients with DVT

It is known that CDT can reduce the incidence and severity of PTS by dissolving the venous thrombus and restoring venous flow [16]. Lee et al. [34] reported that the rate of patency in patients treated with a CDT in an iliofemoral vein segment was higher than in those who only received anticoagulation treatment during the first 6 months following initial treatment (69.2% vs. 38.5%). However, CDT did not have a higher rate of patency in our study. Due to our small sample, we cannot conclude that CDT has no influence on recanalization. Another reason may be that 3 patients in the CDT group who experienced non-recanalization had a history of relapse DVT, which may influence the effectiveness of CDT.

In the past 40 years, IVCF has been widely used in clinical practice. The rate of IVCF implantation increased up to 10~32% in recent years [35]. Another study showed that the risk for recurrence DVT was 1.6 times higher in patients with IVCF

implantation compared to those without it [36]. In the present study of 174 DVT patients, 25 patients underwent IVCF implantation (14.4%). However, the univariate analysis showed that IVCF implantation and PE had no influence on DVT resolution ($P>0.05$).

Limitation

This was a prospective nonrandomized study; thus, our conclusions may have low statistical power. Second, the maximum 6-month follow-up period of this study is not adequate to detect the long-term frequency of recanalization in patients with DVT. Third, despite the simplicity of our study design, our patient cohort was small. Nevertheless, further research is underway with a larger number of patients who will be followed for a longer period of time to acquire more data to support the assertion made based on the findings of the current study.

Conclusions

Short-term anticoagulant therapy and thrombus location at the initial DVT episode may be independent risk factors for delayed recanalization DVT within 6 months of initial treatment. Our study shows higher rates of DVT recanalization with oral anticoagulation therapy duration more than 3 months. Therefore, at the onset of DVT, oral anticoagulation therapy duration should be more than 3 months, especially for cases of proximal thrombus.

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