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Original Article

Does Catheter-Directed Thrombolysis Prevent Postthrombotic Syndrome?

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Purpose: The aim of this study is to identify risk factors of postthrombotic syndrome (PTS) and evaluate the efficacy of catheter-directed thrombolysis (CDT) for preventing the development of PTS in patients with lower extremity deep vein thrombosis (DVT).

Materials and Methods: From 2005 January to 2013 December, 139 limbs of 126 patients were included in this study who had the first episode of proximal DVT at the affected limb and who had visited our out-patient clinic. CDT was performed on 55 limbs (39.6%). We achieved complete recanalization in 39 limbs (70.9%) and partial recanalization (residual thrombus <50.0%) in 16 limbs (29.1%). We retrospectively reviewed medical records for possible predictors of PTS.

Results: Median follow-up duration was 83 months (range, 30-136 months). No differences were found between the CDT and non-CDT group in age, gender, duration of symptom, use of anticoagulation and recurrence of DVT. A significantly higher thrombotic burden was observed in the CDT group (P=0.009). In a binary logistic regression model, patients with PTS had significantly higher body mass index (BMI) (odds ratio [OR], 1.303; 95% confidence interval [CI], 1.079-1.574; P=0.006) and longer thrombotic burden involved in ilio-femoro-popliteal DVT (OR, 3.666; 95% CI, 1.093-12.296; P=0.035). CDT did not influence the risk of PTS (P>0.05).

Conclusion: We suggest that CDT is not effective in preventing PTS, while higher BMI and longer thrombotic burden are associated with the development of PTS in patients with DVT.

Key Words: Postthrombotic syndrome, Catheter directed thrombolysis, Venous thrombosis

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INTRODUCTION

Postthrombotic syndrome (PTS) is a most common chronic complication of deep vein thrombosis (DVT). PTS develops due to valvular incompetence and persistent obstruction. This syndrome is characterized by pain, swelling, a sensation of heaviness, and cramping in the leg [1]. In severe PTS, leg ulcers may develop. While anticoagulation is effective for preventing thrombus extension and recurrence, many patients develop venous incompetence resulting in PTS [2]. PTS develops in 25% to 50% of proximal DVT patients [3,4], despite the use of anticoagulant therapy [5]. Ten percent of PTS patients have moderate PTS and 3% to 5% have severe PTS at 24 months [2]. For many years,

PTS has been known to be associated with impaired quality of life in DVT patients, and as having an influence on patient morbidity [4,6-8].

Several studies have shown that catheter-directed thrombolysis (CDT) is effective for a significant reduction in the incidence of PTS [9-11]. However, its efficacy is controversial, and recent studies have shown that CDT cannot prevent PTS [12]. CDT is also associated with mortality and bleeding risk [11,13]. Studies of the risk factors of PTS are restricted, and we only know that PTS is more common in patients with a proximal DVT [2], recurrent and ipsilateral DVT [3], and an increased body mass index (BMI) [14-16].

The aim of this study is to evaluate the efficacy of CDT for preventing the development of PTS in patients with lower extremity DVT.

MATERIALS AND METHODS

1) Patients

We retrospectively reviewed a patient database in Yeungnam University Medical Center from January 2005 to December 2013. DVT was diagnosed with duplex ultrasonography or computed tomography. Excluding isolated calf vein thrombosis and recurred DVT, 260 limbs of 228 patients were diagnosed as a proximal DVT for the first time. Among them, 126 patients who had undergone the Villata scale's assessment were enrolled in this study, with a total of 139 limbs. PTS was defined as Villata score ≥5 points [17].

2) Treatment

Regarding treatment, all patients received long-term anticoagulation therapy, except three patients who had high bleeding risk. CDT was performed on 55 (39.6%) of the 139 limbs. Indications of CDT were (1) symptom onset time was less than 2 weeks, (2) imaging studies indicate that venous thrombosis had occurred within the past 14 days, and (3) the patients had no bleeding risk. A self-expandable stent was placed if iliac vein stenosis ≥50% was detected after CDT. Outcomes of CDT were as follows: complete lysis in 70.9% (39/55), incomplete lysis (50.0%-99.0%) in 25.5% (14/55), and no lysis (<50.0%) in 3.6% (2/55). An Iliac vein stent was placed in 50.9% of the patients (28/55).

Table 1. Patient demographic and clinical data

Variable	CDT (–) (n=84)	CDT (+) (n=55)	Total (n=139)	P-value
Age (y)	63.0	58.0	62.0	0.165[b]
Male	43 (51.2)	28 (50.9)	71 (51.1)	0.974[a]
Body mass index (kg/m^2)	24.8	24.7	24.7	0.808[b]
Symptom duration (d)	4.5	3.0	4.0	0.893[b]
Symptom duration ≤2 weeks	67 (79.8)	48 (87.3)	115 (82.7)	0.252[a]
Side (left)	54 (64.3)	44 (80.0)	98 (70.5)	0.047[a]
Risk factors of DVT				
Malignancy	10 (11.9)	4 (7.3)	14 (10.1)	0.375[a]
Immobility	28 (33.3)	5 (9.1)	33 (23.7)	0.001[a]
Surgery	24 (28.6)	11 (20.0)	35 (25.2)	0.255[a]
Trauma	15 (17.9)	6 (10.9)	21 (15.1)	0.263[a]
Estrogen	1 (1.2)	5 (9.1)	6 (4.3)	0.036[c]
Pregnancy	2 (2.4)	0 (0)	2 (1.4)	0.518[c]
History of DVT	6 (7.1)	5 (9.1)	11 (7.9)	0.753[c]
Thrombophilia	3 (3.6)	5 (9.1)	8 (5.8)	0.264[c]
Recur during follow-up	6 (7.1)	0 (0)	6 (4.3)	0.081[c]
Extent of thrombus				0.001[a]
Ilio-femoral	30 (35.7)	11 (20.0)	41 (29.5)	
Femoro-popliteal	54 (64.3)	44 (80.0)	98 (70.5)	
Ilio-femoro-popliteal	19 (22.6)	24 (43.6)	43 (30.9)	
Anticoagulation	81 (96.4)	55 (100.0)	136 (97.8)	0.277[c]
Villlata score >5	11 (13.1)	6 (10.9)	17 (12.2)	0.905[a]

Values are presented as median or number (%).
DVT, deep vein thrombosis; CDT, catheter directed thrombolysis.
[a]Chi-square test, [b]Mann-Whitney U test, [c]Fisher-exact test.

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3) Statistical analyses

All data were analyzed using the IBM SPSS Stastistics ver. 22.0 software (IBM Co., Armonk, NY, USA). When comparing the differences of modalities between the two treatment groups, we used a chi-squared test and Fisher-exact test. The differences in continuous data were analyzed using Student's t-test or Mann-Whitney U-test when data were not normally distributed. A binary logistic regression model was used to identify the independent risk factors of development of PTS. Statistical significance was defined as $P<0.05$.

RESULTS

Patient demographic and clinical data are shown in Table 1. The median age of patients was 62 years old and 50.8% were male. Eighty-three percent of patients was acute DVT, with a symptom duration of ≤2 weeks. Left leg involvement was more common in the CDT group. The number of patients with thrombosis from iliac vein to popliteal vein was also significantly higher in the CDT group than in the non-CDT group (44.0% vs. 23.0%, P=0.009). When risk factors of DVT were compared between the two groups, no significant difference was found in the prevalence of risk factors, except immobility and use of estrogen.

During median follow-up at 83 months (range, 30-136 months), PTS had developed in 12 patients. The prevalence of PTS did not differ between the CDT group and the non-CDT group (10.9% [6/55] vs. 13.1% [11/84], P=0.905)

Univariate analyses did not show any significant risk factors related with development of PTS (Table 2). In the multivariate analysis, high BMI (odds ratio [OR], 1.303; 95% confidence interval [CI], 1.079-1.574; P=0.006) and ilio-femoro-popliteal DVT (OR, 3.666; 95% CI, 1.093-12.296; P=0.035) were independent risk factors of the development of PTS (Table 3).

DISCUSSION

Several risk factors are known for developing PTS. Recent studies show recurrent ipsilateral DVT [3,18,19] and increased BMI [14,15,20] are associated with the development of PTS. Location of the primary DVT [12,21] and residual DVT [22,23] is also another risk factor. Proximal distribution of DVT is reportedly a higher risk of PTS [2,14,16].

In this study, high BMI (OR, 1.303; 95% CI, 1.079-1.574;

Table 2. Univariate analysis: risk factors of the development of PTS

Variable	PTS (–) (n=122)	PTS (+) (n=17)	P-value
Age (y)	61.5	62.0	0.966[a]
Male	62 (50.8)	9 (52.9)	0.502[a]
Body mass index (kg/m^2)	24.5	25.8	0.201[b]
Symptom duration ≤2 weeks	104 (85.2)	11 (64.7)	0.385[a]
Side (left)	86 (11)	12 (70.6)	1.000[a]
Risk factors of DVT			
Malignancy	12 (9.8)	2 (11.8)	1.000[a]
Immobility	30 (24.6)	3 (17.6)	1.000[a]
Surgery	31 (25.4)	4 (23.5)	1.000[a]
Trauma	17 (13.9)	4 (23.5)	0.656[a]
Estrogen	4 (3.3)	2 (11.8)	1.000[c]
History of DVT	10 (8.2)	1 (5.9)	0.582[c]
Thrombophilia	7 (5.7)	1 (5.9)	1.000[c]
Recur during follow-up	6 (4.9)	0 (0)	1.000[c]
Extent of thrombus			0.112[a]
Ilio-femoro-popliteal	35 (28.7)	8 (47.1)	
Others	87 (71.3)	9 (52.9)	
Anticoagulation	120 (98.4)	16 (94.1)	0.328[c]
Catheter directed thrombolysis	49 (40.2)	6 (35.3)	0.729[c]
Iliac vein stenting	30 (24.6)	1 (5.9)	0.195[c]

Values are presented as median or number (%).
PTS, postthrombotic syndrome; DVT, deep vein thrombosis.
[a]Chi-square test, [b]Mann-Whitney U test, [c]Fisher-exact test.

Table 3. Multivariate analysis: risk factors of the development of postthrombotic syndrome

Variable	Relative risk	95% confidence interval	P-value
Age	1.303	0.962-1.044	0.915
Male	0.926	0.280-3.066	0.900
Body mass index	1.303	1.079-1.574	0.006
Left side	0.849	0.231-3.119	0.805
Catheter directed thrombolysis	1.317	0.367-4.728	0.673
Iliac vein stenting	0.184	0.017-1.983	0.163
Symptom duration >2 weeks	2.934	0.816-10.546	0.099
Ilio-femoro-popliteal deep vein thrombosis	3.666	1.093-12.296	0.035

P=0.006) and extensive thrombus burden (OR, 3.666; 95% CI, 1.093-12.296; P=0.035) increased the risk of PTS development. The pathophysiology of PTS has not been fully determined. PTS develops as a result of venous pressure, which is caused by venous obstruction, valvular incompetence, or both. A venous obstruction is injurious to vein walls as it promotes the inflammatory process [24]. The risk of vessel damage increases as the length of the thrombus is in contact with the vein wall increases [25]. This could be reflected in the result of our study since extensive thrombus burden is a risk factor of PTS. Early elimination of thrombus may preserve valvular function and prevent fibrosis, a sequela of chronic thrombus [26]; hence, CDT has been considered as a treatment for the prevention of PTS. However, we were not able to prove that CDT can prevent PTS. The prevalence of PTS was 10.9% at the CDT group and 13.1% at the non-CDT group (P=0.905). PTS development was not associated with CDT.

In the CaVenT trial, 189 patients (90.4% of the 209 patients originally randomized) with a first time ilio-femoral DVT were included within 21 days from the symptom onset who were included in the CDT group and control group [9,10]. The development of PTS in the CDT group had an absolute risk reduction of 14.4% after 2 years and 28.0% after 5 years of follow-up compared with standard treatment. The long-term beneficial effect of preventing PTS in CDT increased with time.

The Cochrane Library reported that the thrombolysis group showed improvement in venous patency. The review enrolled 17 controlled trials that randomized a total of 1,103 people. At up to five years after follow-up, the thrombolysis group was reported to have significantly less PTS (relative risk [RR], 0.66; 95% CI, 0.53-0.81; P<0.0001), but those receiving thrombolysis had increased bleeding complications (RR, 2.23; 95% CI, 0.41-3.52; P=0.0006) [11].

In the recent Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study, in which 692 patients were enrolled from 56 clinical centers in the United States, the addition of pharmacomechanical CDT to anticoagulation did not show any reduction in the risk of the PTS over a follow-up of 2 years (47.0% in the pharmacomechanical-thrombolysis group and 48.0% in the control group; RR, 0.96; 95% CI, 0.82-1.11; P=0.560). The addition of pharmacomechanical CDT to anticoagulation resulted in a higher risk of major bleeding [12]. The size of the ATTRACT study was larger than that of the catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (CaVenT) study (692 patients vs. 209 patients, respectively). In addition, in the CaVenT study, a conventional catheter was used, while pharmacomechanical thrombolysis was used in the ATTRACT trial.

According to the result of the ATTRACT study, a meta-analysis was performed on 6 comparative studies and 4 randomized controlled trials including the ATTRACT trial and the CaVenT study [27]. That meta-analysis showed that pharmacomechanical thrombolysis improved the patency or the severity of the ilio-femoral vein (95% CI, 2.36-4.67; I^2=44.0%, P<0.00001) and reduced the risk of PTS (95% CI, 0.51-0.82; I^2=78.0%, P=0.0002) compared with anticoagulation therapy alone; however, CDT was not shown to prevent mild PTS (95% CI, 0.74-1.39; I^2=79.0%, P=0.910) in the subgroup analysis of randomized controlled trials, CDT was not shown to prevent PTS (95% CI, 0.65-1.10; I^2=59.0%, P=0.200). There was also a statistically significant increase in bleeding complication in this study (95% CI, 1.91-3.04; I^2=33.0%, P<0.00001).

Based on previous studies, it is difficult to conclude that CDT can help prevent PTS and it is still controversial.

Although this study has some limitations, such as retrospective design and relatively small sample size, it was shown that PTS could not reduce PTS development.

In conclusion, we suggest that a higher BMI and longer thrombotic burden are associated with the development of PTS in patients with DVT and that CDT is not effective in preventing PTS.

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