Beneficial Effect of Endovascular Treatment on Villalta Score in Japanese Patients With Chronic Iliofemoral Venous Thrombosis and Post-Thrombotic Syndrome

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Background: Post-thrombotic syndrome (PTS), the most common complication of deep venous thrombosis (DVT), develops in ≥50% of patients with iliofemoral DVT. However, the benefit of endovascular treatment in Japanese patients with chronic DVT and PTS remains unclear.

Methods and Results: Between June 2014 and May 2016, endovascular treatment was performed in 11 consecutive Japanese patients with chronic iliofemoral DVT and PTS refractory to anticoagulant therapy and elastic compression stockings. We evaluated the technical success rate, complications, patency, Villalta score, calf circumference, and popliteal vein reflux in both the acute stage (the day following endovascular treatment) and chronic stage (after 6 months). Imaging follow-up included venous duplex scanning and/or magnetic resonance venography. The technical success rate was 81.8%, without complications. In patients with successful intervention, the Villalta score improved significantly, from 9.0 ± 3.7 preoperatively to 3.6 ± 2.5 in the acute phase (P < 0.01) and 2.9 ± 2.1 in the chronic phase (P < 0.001). The bilateral difference in lower thigh circumference also improved significantly, from 2.6 ± 1.0 cm preoperatively to 1.4 ± 1.0 cm in the chronic phase (P < 0.001). However, popliteal vein reflux did not improve. In patients with successful intervention, venous patency rate was 100% at 6 months post-intervention.

Conclusions: Endovascular treatment is safe and effective in Japanese patients with chronic iliofemoral DVT and PTS.

Key Words: Chronic iliofemoral venous thrombosis; Endovascular treatment; Post-thrombotic syndrome

Deep venous thrombosis (DVT) is a major healthcare and socioeconomic problem, with a yearly incidence of 115.5 cases per 1,000,000 individuals in Japan. Post-thrombotic syndrome (PTS), the most common and feared long-term complication of DVT, is characterized by pain, swelling, venous claudication, edema, and skin deterioration, including venous ulcers in severe cases. PTs develops within 2 years in more than 50% of patients with proximal DVT, despite widespread use of anticoagulant therapy. Although the pathogenesis of PTS is unclear, it is believed that persistent venous outflow obstruction, chronic venous insufficiency, impaired venous microcirculation, and sometimes extrinsic obstructions secondary to malignancy or iliac compression syndrome play an important role in its clinical expression. Residual thrombosis after acute proximal DVT treatment has been shown to be a strong predictor of PTS. PTS increases healthcare costs and reduces quality of life. Therefore, endovascular therapies such as aspiration thrombectomy, balloon angioplasty with or without stenting, and catheter-directed thrombolysis of acute proximal DVT are considered for the prevention of PTS. Although no evidence-based treatment has been established for PTS, elastic compression stocking (ECS) therapy has been considered the mainstay for reducing symptoms in patients with PTS, presumably because of its availability and safety. Some studies have suggested that surgical procedures reduce severe PTS symptoms, but no such investigations have provided data consistent with Level of Evidence A. Some recent studies reported that endovascular treatment alleviates symptoms in patients with severe PTS, with encouraging technical success rates, as well as mid- and long-term clinical and stent outcomes. However, only limited data are available, and thus the benefit of endovascular treatment in PTS patients remains unclear, especially in the Japanese population.

The aim of the present study was to assess the effectiveness and safety of endovascular treatment in Japanese patients with chronic iliofemoral venous thrombosis and persistent PTS symptoms despite treatment with anticoagulants and ECS therapy for PTS.

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Endovascular Procedure
Endovascular treatment was performed in patients with persistent PTS symptoms caused by chronic stenotic and/or occlusive iliofemoral venous thrombosis despite treatment with anticoagulants and ECS therapy. We defined as significant those venous lesions with complete occlusion or with >50% stenosis detected on venography (Figure 1A).

Under ultrasonographic guidance and using a local anesthetic, we punctured the affected ipsilateral common femoral vein or popliteal vein. After an 8Fr catheter sheath was placed in the vein, systemic intravenous heparinization was achieved using 2,000U of unfractionated heparin. A guidewire was used to pass the catheter through the occluded or stenotic lesions of the iliofemoral vein. After performing intravascular ultrasonography (IVUS imaging catheter; Volcano Corp., San Diego, CA, USA), we determined the optimal size of the balloon as 1 size smaller than the distal diameter of the reference vessel. Balloon angioplasty was performed using 6–9-mm semicompliant balloons (Figure 1B). Balloon angioplasty was performed until venous flow improved without delay (Figure 1C). Additional treatment with stenting to alleviate iliac compression was performed if venous flow after ballooning was delayed, after obtaining informed consent from the patients. In 2 patients with iliac compression, a self-expanding stent (10×100-mm Luminexx stent from C.R. Bard, Murray, NJ, USA in 1 patient; 9×100-mm Epic stent from Boston Scientific, Marlborough, MA, USA in 1 patient) was placed in the common iliac vein and post-dilatation was performed using 7–8-mm balloons. Stent size was determined by IVUS measurements after ballooning. We chose the stent diameter as 1 mm larger than the distal diameter of the reference vessel. All patients were hospitalized overnight and returned to their normal daily activities the next morning. Anticoagulant therapy and ECS therapy were continued throughout the follow-up.

Methods

Patient Selection
Between June 2014 and May 2016, 15 consecutive patients with chronic stenotic and/or occlusive venous thrombosis and several symptoms of chronic venous disease received endovascular treatment. Patients with upper-limb venous thrombosis (n=1) and lower-limb venous thrombosis (n=3) without PTS, which was defined as Villalta score <4, were excluded. Finally, we retrospectively reviewed the clinical data of 11 consecutive patients with chronic iliofemoral venous thrombosis and PTS.

Definition of Chronic DVT and PTS
Before undergoing endovascular treatment, all patients had been diagnosed as having DVT by ultrasound duplex scan and computerized tomography venography or magnetic resonance venography (MRV). We defined chronic DVT as DVT diagnosed by the means just described and previously treated with anticoagulant therapy for more than 6 months. Prior to endovascular treatment, each patient had been prescribed ECS (30 mmHg at the ankle).

To define PTS and evaluate its severity, we used the Villalta score, which is commonly used for this purpose and recommended by the American Heart Association. The Villalta score is also useful for evaluating quality of life. Falcoz et al reported that an increase in Villalta score was an independent risk factor for decreased quality of life as evaluated by the Chronic Venous Insufficiency Questionnaire (CIVIQ-20). The Villalta score, which is a validated and reliable clinical tool for measuring PTS, incorporates the assessment of 5 subjective venous symptoms (pain, cramps, heaviness, paresthesia, and pruritus) and 6 objective venous signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression), as well as the presence or absence of skin ulcers in the DVT-affected leg. Each evaluation item is scored from 0 to 3, with a total score of 0–3 indicating no PTS, 5–9 indicating mild PTS, 10–14 indicating moderate PTS, and ≥15 or presence of venous ulcers regardless of score indicating severe PTS.

Figure 1. Representative venography in a patient with successful endovascular treatment (case 11) among a group of Japanese patients with chronic iliofemoral deep venous thrombosis and post-thrombotic syndrome refractory to anticoagulant therapy and elastic compression stockings. (A) Before treatment, a severe stenotic lesion (arrow) can be seen in the iliac vein on digital angiography. (B) Digital angiogram obtained during ballooning with 6-mm semicompliant balloons. (C) Digital subtraction angiogram obtained after ballooning.
Endovascular Treatment for Chronic DVT

Endpoints

Assessment of Procedural Success  We defined procedural technical success as the successful ballooning or stenting of the occluded or stenotic lesion. If the guidewire could not be passed through the occluded lesions and balloon angioplasty was abandoned, the procedure was deemed unsuccessful. We assessed the safety of the endovascular procedure in terms of the incidence of treatment-related complications, including vessel perforation by the wire, minor or major bleeding, infection, allergic reaction, renal failure, extension of thrombosis, pulmonary embolism, and death.

Outcomes of Endovascular Treatment  The outcome of endovascular treatment was assessed in terms of the Villalta score, calf circumference, popliteal vein reflux, and patency of the treated vein. The Villalta score and calf circumference were assessed in the acute phase (i.e., the day after the procedure) and in the chronic phase (at 6 months after the procedure). Calf circumference was measured at 10 cm below the tibial tuberosity, and the difference between the value obtained in the symptomatic leg and that obtained in the asymptomatic leg (i.e., bilateral difference in calf circumference) was calculated. Popliteal vein reflux was also evaluated by ultrasonic duplex scanning before and at 6 months after endovascular treatment. Popliteal vein reflux was defined as a clear flow retrograde to the direction of physiological flow, lasting for >0.5 s. Vein patency was evaluated on MRV at 6 months after the procedure.

Statistical Analysis

Statistical analysis was performed using JMP8 (SAS Institute, Cary, NC, USA). Quantitative variables are expressed as mean ± standard deviation. Changes in the Villalta score and the bilateral difference in calf circumference were compared using a paired t-test. P-values <0.05 were considered to indicate statistical significance. This study was approved by the Review Board of the National Cerebral and Cardiovascular Center.

Results

Patients' Characteristics  Between June 2014 and May 2016, 11 endovascular treatments were performed in 11 patients with chronic DVT and PTS (5 men and 6 women; median age, 41 years; age range, 31–75 years) (Table). The median duration from PTS symptom onset to endovascular treatment was 42 months (range, 6–273 months); 4 patients (36%) had complete occlusion and 7 patients (64%) had severe stenotic lesions in the iliofemoral vein. The left leg was affected in 10 patients (91%). Table gives an overview of the location of thrombosis. There were no thromboses in the superficial vein.

Table. Baseline Characteristics of 11 Patients With Chronic DVT and PTS

<table>
<thead>
<tr>
<th>Case no.</th>
<th>AC therapy</th>
<th>Villalta score</th>
<th>Presence of skin ulcer</th>
<th>Presence of venous claudication</th>
<th>Bilateral difference in lower thigh circumference</th>
<th>Venous dysfunction</th>
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<tr>
<td>1</td>
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<td>WF</td>
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<td>7</td>
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Unsuccessful procedure in cases 2 and 8. AC, anticoagulant; BMI, body mass index; CFV, common femoral vein; CIV, common iliac vein; DOAC, direct oral anticoagulant; DVT, deep venous thrombosis; EIV, external iliac vein; IC, iliac compression; L, left; ND, not determined; POP, popliteal vein; PTS, post-thrombo-embolic syndrome; R, right; WF, warfarin.
or perforator vein, and no varicose veins.

All patients were examined for risk factors of DVT, such as thrombophilia and cancer: 8 patients (73%) had ≥1 risk factors of DVT. Importantly, 1 patient had thrombophilia (protein S deficiency with iliac compression), 1 had prolonged immobility with iliac compression, 1 used steroids, 3 had iliac compression, and 2 were pregnant and had iliac compression.

All patients had venous claudication, but none had skin ulcers in the affected leg. PTS was severe in 2 patients, moderate in 4 patients, and mild in 5 patients; 6 (55%) patients had calf swelling (bilateral difference in calf circumference >3 cm; measured at 10 cm below the tibial tuberosity). Venous function was evaluated in 9 of 11 patients, as the remaining 2 patients could not undergo such evaluation because of popliteal vein thrombosis: 6 of the 9 patients evaluated had venous dysfunction consisting of popliteal vein reflux detected by ultrasound duplex scanning. During follow-up, anticoagulant therapy was prescribed in all patients (warfarin in 6 patients and DOACs...
in 5 patients), at the discretion of the attending physician.

**Procedural Success and Vein Patency**

The procedural success rate was 81.8% (9/11). In the 9 patients with successful treatment, we used 6–9-mm balloons for balloon angioplasty. Representative scans obtained in a patient with successful treatment are shown in Figure 1 and Figure 2. The segment of the left external iliac vein originally presenting a severely stenotic lesion (Figure 2A) remained patent at 6 months after recanalization (Figure 2B). In 2 of the 9 patients with successful treatment (1 with occluded lesions, 1 with severe stenotic lesions), self-expanding stents (diameter, 9–10 mm; length, 100 mm) were placed in the iliac vein to alleviate iliac compression, and post-dilatation was performed using 7–8-mm balloons. There were no complications associated with the endovascular treatment.

**Outcomes of Endovascular Treatment**

The changes in Villalta score and bilateral difference in calf circumference in patients with successful endovascular treatment (n=9) are summarized in Figure 3 and Figure 4. The Villalta score improved significantly from 9.0±3.7 (range, 5–15) at baseline to 3±2.5 (range, 1–7) in the acute phase (P<0.01) and to 2.9±2.1 (range, 0–7) in the chronic phase (P<0.001). The severity of PTS before and at 6 months after endovascular treatment is summarized in Figure 5. The symptoms resolved entirely (i.e., Villalta score 0–4, indicating no PTS) in 8 of the 9 patients with successful treatment (89%); in the remaining patient, symptoms improved from severe to mild PTS (Villalta score changed from 15 to 7). Particular items of the Villalta score were analyzed separately (i.e., pain and edema, which were often the chief complaint). Pain median score improved from 1 (range, 0–2) at baseline to 0 (range, 0–1) in the acute stage and 0 (range, 0–1) in the chronic stage (P<0.05 for both comparisons). Only 1 patient continued to have pain (score=1). The bilateral difference in calf circumference improved significantly, from 2.6±1.0 cm (range, 1–4 cm) at baseline to 1.8±1.1 cm (range, 0–3 cm) in the acute phase (P=0.04) and to 1.4±1.0 cm (range, 0–3 cm) in the chronic phase (P<0.001). The bilateral difference in calf circumference correlated well with the Villalta score for edema, which improved from 0.78±0.8 (median, 1; range, 0–2) in the acute phase (P=0.03) and to 0.67±0.7 (median, 1; range, 0–1) in the chronic phase (P<0.01). Edema resolved completely in 3 of the 9 patients with successful endovascular treatment (33.3%).

In 1 patient, we could not evaluate venous function at baseline because of popliteal vein thrombosis. Of the remaining 8 patients with procedural success, 5 (63%) had venous dysfunction at baseline, which did not improve after endovascular treatment. On the other hand, venous function did not worsen after treatment in the other 3 patients evaluated (i.e., those without venous dysfunction at baseline). Additionally, popliteal vein reflux was not affected by endovascular treatment. No in-stent thrombosis events and no recurrent DVT were recorded at the 6-month follow-up.

**Discussion**

The 2009 Japanese guidelines for DVT treatment25 and the 2014 American Heart Association (AHA) guidelines4 recommended that percutaneous endovenous recanalization (e.g., stent or balloon angioplasty) may be considered in severely symptomatic patients with an occluded iliac vein or vena cava, without specifying the timing of endovascular treatment (e.g., the acute or chronic phase). The key aspects of the present study were as follows. First, the definitions of chronic DVT and PTS, as well as the criteria for endovascular treatment indication, are objective and clearly described. Second, most of our patients had mild-to-moderate PTS, and ballooning (rather than stenting) was the main endovascular treatment strategy used, with satisfactory outcomes and no requirement for long-term anticoagulant or antiplatelet treatment. Therefore, our findings that endovascular treatment can be applied regardless of PTS severity are not only interesting, but also very useful in the clinical setting. Preliminary studies have reported encouraging technical success rates, as well as mid- and long-term clinical and stent outcomes of endovascular treatment in patients with PTS and iliofemoral obstruction.9,11,21,24,26,28 However, several important aspects of those previous studies have not been clarified, especially regarding the definition of the target disease and the indication for endovascular treat-
ment. First, the definition of chronic DVT and the clinical criteria for PTS were not unified, because of the wide spectrum of symptoms and dynamic changes over time. Therefore, in the present study, we defined chronic DVT specifically as residual DVT despite anticoagulant therapy for more than 6 months. However, PTS has been evaluated using various tools including the Clinical, Etiological, Anatomic, Pathophysiological classification, venous clinical severity score, and Villalta score. Because the AHA recently recommended the sole use of the Villalta score for establishing the PTS diagnosis, we used it to diagnose PTS and evaluate the curative effect of endovascular treatment in the present study. It should be also noted that previous studies did not provide a detailed description of the indication for endovascular treatment in patients with chronic DVT and PTS. We defined “chronic DVT” and “PTS” as given in the Methods, and importantly, the indication for endovascular treatment was finally determined as targeting chronic venous lesions with complete occlusion or >50% stenosis, based on venography.

Several reports have assessed multiple aspects, including technical success, vein patency, and endovascular treatment outcomes consisting of the Villalta score, calf circumference, and popliteal vein reflux. Sarici et al reported a significant decrease in Villalta score after stenting, from 18 (range, 7–30) at baseline to 8 (range, 4–19) at 6 months post-intervention, as well as improvement in calf circumference at 1 month post-intervention. Others also reported that the Villalta score decreased from 22.0 at baseline to 9.3 after stenting, and from 14 (range, 11–22) at baseline to 5 (range, 1–10) at 3 months after the procedure. In our study, the Villalta score improved significantly after endovascular treatment, from 9 (±3.7) (range, 5–19) at baseline to 2.9 (±2.1) (range, 0–7) at 6 months after procedure (P<0.001), which is consistent with previous observations. However, our study differs from previous investigations in terms of the severity of PTS at baseline and shows satisfactory outcomes in selected patients predominantly showing mild-to-moderate PTS (9 of 11 patients treated; 82%). These findings indicated that endovascular treatment is an effective treatment option in patients with residual symptoms, independent of PTS severity.

A recent meta-analysis reported 1-year stent patency rates of 79% in chronic post-thrombotic patients, as evaluated by duplex ultrasonography. In our study, 7 of 9 patients with procedural success (78%) were treated only with ballooning, whereas the remaining 2 patients (12%) received a stent and showed vein patency at 6 months post-intervention. Neglen et al reported 5-year stent patency rates of 67%. Falcoz et al reported that 14.3% of patients (3/21) had early in-stent thrombosis (at 2 months post-intervention) despite receiving dual therapy with antivitamin K anticoagulant and antiplatelet drug for 3 months. Furthermore, accumulated evidence demonstrated that the treatment of acute DVT with DOACs rather than with warfarin was associated with a numerically lower but statistically non-significant risk of PTS. Currently, in patients with chronic iliofemoral venous thrombosis and PTS, there is no guideline specifying the optimal duration of anticoagulant and/or antiplatelet therapy after endovascular treatment with or without stenting, or the optimal choice of drugs (e.g., antivitamin K anticoagulant, DOAC, or antiplatelet therapy). Indeed, early and late in-stent thrombosis despite treatment with antivitamin K anticoagulant, antiplatelet drugs, or dual therapy with antivitamin K anticoagulant and antiplatelet drug was one of the main complications after iliac vein stenting. Long-term anticoagulant or antiplatelet treatment (even dual or triple therapy) does not necessarily help decrease the risk of in-stent thrombosis or thromboembolic events but may cause hemorrhagic complications. Our findings suggested that endovascular treatment with ballooning alone is a safe and effective option in chronic DVT patients with residual symptoms, with good venous patency and no requirement for long-term anticoagulant or antiplatelet treatment.

Study Limitations
Specifically, the number of patients was small, follow-up duration was short, and long-term outcomes remained uncertain. Second, our study did not include a control group, so we could not compare the outcomes between the intervention group and the control group. In particular, it is not clear why endovascular treatment could improve venous outflow obstruction but not venous function. Previous studies showed that endovascular treatment alleviated PTS symptoms and improved long-term stent patency but did not improve venous valve function, which is consistent with our present findings. Some patients are expected to experience long-term recurrence of venous symptoms, in which case neovalve construction to improve valve competence may represent a good therapeutic strategy. Finally, in this study, we did not include superficial vein and perforator surgery in the treatment strategy. In general, superficial and perforator surgery should be considered in primary chronic venous insufficiency (CVI) and is not recommended in secondary CVI caused by DVT. However, superficial and perforator vein surgery is also an alternative therapy to improve venous valve competence and reflux or significant superficial varix with reflux in secondary CVI patients. At patient check-up in our study, however, none showed leg ulceration or varicose veins. Moreover, they had only significant stenotic and/or occlusive lesions with residual chronic DVT.

Conclusions
Our findings clearly indicated that endovascular treatment is a safe and effective option for Japanese patients with residual symptoms despite anticoagulant therapy and ECS therapy, and can be performed regardless of PTS severity.

Grants / Conflict of Interest / Acknowledgments

None.

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