⫸ *Original Article* ⫷

Asymptomatic Isolated Calf Deep Vein Thrombosis: Does It Worsen after Varicose Vein Surgery?

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In our varicose vein center, on a trial basis, among the patients with asymptomatic calf deep vein thrombosis (CDVT) we carefully selected the patients for varicose vein surgery using the requirements as follows; 1) the patients had varicose veins with incompetent saphenous veins, 2) sequential examination including DUS confirmed stability and clinical insignificance of asymptomatic CDVT, 3) the patients do not have any risk factors for DVT such as a coagulation profile disorder (antithrombin deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome) or malignancies, 4) surgery is possible under local anesthesia alone, and 5) the patients can understand the concept of asymptomatic CDVT and undergo the surgery on their own will and informed consent. The patients who fulfilled these conditions underwent the varicose vein surgery. Twenty-eight patients with 30 limbs with varicose veins had asymptomatic CDVT, found by preoperative duplex ultrasonography (DUS). Among CDVT, 91% of CDVT existed in the soleal veins. After the diagnosis of the asymptomatic CDVT, serial DUS was performed and showed no changes in the status of the thrombus. Then varicose vein surgery (high ligation of the saphenous junctions either with or without stripping of the saphenous veins) was performed. After the surgery, the CDVT was re-evaluated by DUS. In 27 limbs, CDVT did not show any changes in the status of the thrombus, and in 3 limbs the CDVT was partially resolved. These data suggest that, at least, as far as the patients fulfilled these conditions, varicose vein surgery did not worsen the asymptomatic CDVT. (This is a translation of Jpn J Phlebol 2016; 27: 405–412.)

Keywords: deep vein thrombosis, varicose veins, stripping, soleal veins

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Introduction

Screening for deep vein thrombosis (DVT) is necessary prior to varicose vein (VV) surgery. Formerly, venography was the gold standard to investigate the venous system in lower extremities[1]; however, nowadays duplex ultrasonography (DUS) is used for initial examination imaging of the venous system, as it is less invasive and more useful for detecting DVT in the soleal veins than venography.[2] The increasing number of cases with asymptomatic DVT, especially distal DVT, was incidentally recognized during use of DUS to investigate the venous system.[3,4] However, no consensus has been reached on whether or not indications for VV surgery include the presence of incidental distal DVT (IDDVT).[1] When venography was the gold standard for DVT screening, VV surgery was contraindicated in patients with DVT.[1] Current guidelines in Japan define treatment with endovenous ablation as a contraindication for patients with VVs when DVT are detected, even incidentally.[5] On the other hand, indication for VV surgery involving high ligation of the junction between the saphenous veins (SVs) and deep veins, either with or without stripping, remains unclear in VV patients with IDDVT.[1] Therefore, we carefully selected VV patients with IDDVT using the following criteria and performed high ligation of the SV junction with or without stripping. The criteria included: (1) patients with VVs with incompetent SVs, (2) stability and clinical insignificance of IDDVT confirmed by serial DUS, (3) patients without risk factors for DVT, (4) VV surgery possible under local anesthesia, and (5) patients able to understand the concept of IDDVT. We aimed to clarify whether IDDVT in these patients worsened after VV surgery, and performed preoperative and postoperative serial imaging using DUS to evaluate the status of IDDVT.

Materials and Methods

Ethics

The study protocol was approved by the local ethics committee of Aisei Hospital and written informed consent was

obtained from all participants.

Study participants

Participants were patients attending the varicose vein center of Aisei Hospital with complaints of VVs from January 2013 to December 2015.

Inclusion and exclusion criteria

We included patients diagnosed with primary VVs due to SV incompetence without any signs of DVT. The VVs were diagnosed by board-certified vascular specialists. The patients underwent DUS screening for DVT before VV surgery, by a single, certified clinical vascular technologist using HI VISION Preirus (Hitachi Aloka Medical, Ltd., Tokyo, Japan), according to a standardized examination protocol for DVT screening in our hospital. DUS revealed IDDVT preoperatively in VV patients. IDDVT was evaluated by laboratory examination (D-dimer value and coagulation profile disorder, i.e., antithrombin (AT) deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome), as well as serial DUS 3 months after the time of first IDDVT diagnosis.

We carefully selected patients with VVs and IDDVT using the following criteria: (1) patients with VVs with incompetent SVs, (2) stability and clinical insignificance of IDDVT confirmed by serial DUS, (3) patients without risk factors for DVT, (4) VV surgery possible under local anesthesia, and (5) patients able to understand the concept of IDDVT. Patients who fulfilled the criteria underwent VV surgery (flush ligation of the SV junction either with or without selective stripping of the incompetent SVs). After VV surgery, IDDVT was reevaluated to determine whether or not the IDDVT worsened postoperatively. Postoperative DUS assessment was carried out initially 1 month after VV surgery, and in some cases, serial DUS was performed thereafter.

Results

Patients

We included 28 patients with 30 affected lower limbs (11 males, 17 females (male:female=1:1.5), aged 31–83

years (mean, 63.1 years). Among the 30 affected limbs (16 right legs/14 left legs)), 27 had VVs due to incompetent great SVs (GSVs), and three were due to incompetent short SVs (SSVs) (**Table 1**). Clinical classifications at the time of referral included 14 limbs in class C2, eight in C3, six in C4a, one in C4b, and one in C6. The patient in class C6 underwent compression therapy until the venous ulcers healed, followed by VV surgery.

Superficial thrombophlebitis (STP)

Among 28 patients with VVs and IDDVT, six patients with six affected limbs had STP (**Table 1**). STP was present in branch type VVs (GSV, four limbs), in the short segment of the incompetent GSV around the knee joint (one limb), and in segmental VVs around the ankle (one limb). None of the six patients with STP had any kind of coagulation profile disorder (i.e., antithrombin deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome). Concerning risk factors for DVT, one patient was taking selective estrogen receptor modulator (SERM) medication for osteoporosis.

IDDVT

Twenty-five patients with 27 affected limbs had high-echogeneic IDDVT, one patient with one affected limb had iso-echogeneic IDDVT, and two patients with two affected limbs had low-echogeneic IDDVT. One patient with iso-echogeneic IDDVT had VVs due to incompetent SSV without STP. The IDDVT existed in the central soleal vein and the D-dimer value was negative (0.6 µg/mL). One patient with low-echogeneic IDDVT had VVs due to incompetent GSV, with STP in branch type VVs. The IDDVT existed in the central soleal vein and the D-dimer value was high (2.5 µg/mL). Another patient with low-echogeneic IDDVT also had VVs due to incompetent GSV, with STP in the branch type VVs. The IDDVT existed in the lateral and medial soleal veins, and the D-dimer value was 1.5 µg/mL.

The locations of the IDDVT are presented in **Table 2**. The central soleal vein had the most cases of IDDVT, with 21 limbs (62%). We also found IDDVT in the medial soleal vein (nine limbs, 26%), lateral soleal vein (one limb, 3%), peroneal vein (one limb, 3%), sural vein (one limb,

Table 1 Asymptomatic calf DVT in the patients with varicose veins

	SV (c)	SV (m)	SV (l)	Peroneal v.	Sural v.	p. tibial v.
GSV: 27 legs	18	9	1	1	1	1
SSV: 3 legs	3	0	0	0	0	0
STP (+): 7 legs	4	2	1	1	0	0
STP (−): 23 legs	17	7	0	0	1	1
Clot reduction after surgery	1	1	0	1	0	0

DVT: deep vein thrombosis; GSV: great saphenous vein; SSV: small saphenous vein; STP: superficial thrombophlebitis; SV: soleal vein; c: central; m: medial; l: lateral; p. tibial: posterior tibial; v.: vein

3%), and posterior tibial vein (one limb, 3%). We did not find IDDVT in the anterior tibial vein.

Patients with high- and iso-echogeneic IDDVT underwent compression therapy alone, without medication, and those with low-echogeneic IDDVT underwent anticoagulation treatment using warfarin (international normalized ratio: 1.5–2.5), as well as compression therapy. Anticoagulation was stopped if serial DUS revealed that residual IDDVT became high-echogeneic; and if the residual IDDVT had not worsened after stopping anticoagulation, the patients underwent VV surgery.

The time from initial diagnosis of IDDVT to VV surgery ranged from 3 to 34 months (mean, 9.4 months). For patients with low-echogeneic IDDVT is ranged from 22 to 27 months. There were no changes in the number or size of IDDVT in any of the 28 patients, except a change in echogeneity (in some patients, the echogeneity of the IDDVT became higher, meaning the IDDVT had been there longer, as measured by DUS). IDDVTs were not resolved in the follow-up period.

The D-dimer values ranged from 0.5 to 3.8 µg/mL (mean, 1.3 µg/mL). None of the patients had any coagulation profile disorders, except one who had a decreased AT level (74%). We determined that liver dysfunction due to the fatty liver caused the slightly decreased AT level in this patient. The other risk factors for DVT are shown in **Table 3**. Three patients had a history of cancer, two had cast immobilization, two were taking antidepressants, two were taking SERM medication, one suffered alcohol abuse, one had liver dysfunction, one was undergoing bed rest, and one had had meniscus surgery.

VV surgery

Twenty-two patients underwent high ligation and inversion stripping of the incompetent GSVs, including nine limbs with InvisiGrip Vein Stripper (LeMaitre Vascular GK, Tokyo, Japan), 12 limbs with a vein stripper (B. Braun Aesculap Japan, Tokyo, Japan), and one limb without a vein stripper (the incompetent GSV was removed in a multiple segmental resections). High ligation and inversion stripping of the incompetent SSV with a vein stripper was performed in two limbs. The high ligation procedure (high ligation of the SV junction without stripping of the SV) was performed in six limbs (five with incompetent GSV and one with incompetent SSV). High ligation of the incompetent GSV consisted of a three-site ligation and division: flush ligation of the saphenofemoral junction, and ligation and division of the GSV in the mid-thigh (usually the connecting points of the perforators of the femoral canal) and in the calf (usually the joining point of the anterior and posterior accessory GSV in the calf). The high ligation procedure of the incompetent SSV consisted of high ligation of the saphenopopliteal junction and division of the SSV. After VV surgery, all patients received postoperative compression using elastic compression stockings for 1 week (all day) and for another 3 weeks thereafter during the daytime.

Postoperative changes in IDDVT status

A DUS 1 month after VV surgery demonstrated that there were no changes in IDDVT, either in size or in echogeneity, in 25 patients with 27 affected limbs. Partial resolution of the IDDVT was observed in three patients with three affected limbs. Among them, DUS 3 months after the VV surgery revealed further regression of the IDDVT

Table 2 Location of DVT in the calf veins

	SV (c)	SV (m)	SV (l)	Peroneal v.	Sural v.	p. tibial v.	a. tibial v.
Legs (%)	21 (62)	9 (26)	1 (3)	1 (3)	1 (3)	1 (3)	0

DVT: deep vein thrombosis; SV: soleal vein; c: central; m: medial; l: lateral; p. tibial: posterior tibial; a. tibial: anterior tibial; v.: vein

Table 3 Risk factors in the patients with asymptomatic calf DVT

	SV (c)	SV (m)	SV (l)	Peroneal v.	Sural v.	p. tibial v.
Past history of cancer	3	0	0	0	0	0
Cast immobilization	1	1	0	0	0	0
Antidepressant	1	1	0	0	0	0
SERM	2	0	0	0	0	0
Alcohol abuse	1	0	0	0	0	0
Liver dysfunction	0	1	0	0	0	0
Bed rest	0	1	0	0	0	0
Meniscus surgery	0	1	0	0	0	0

DVT: deep vein thrombosis; SERM: selective estrogen receptor modulater; SV: soleal vein; c: central; m: medial; l: lateral; p. tibial: posterior tibial; v.: vein
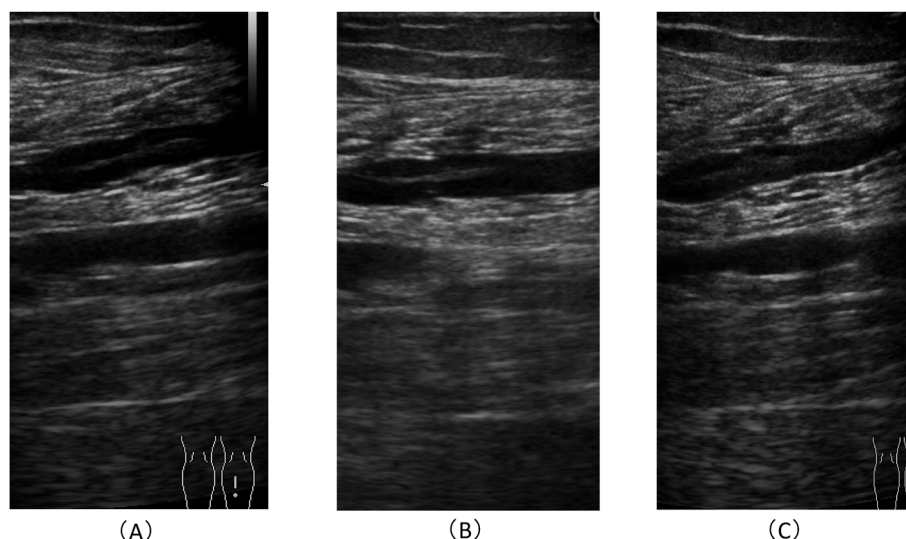
(A) (B) (C)

Fig. 1 Duplex ultrasonography (DUS) showed thrombus with high echogenicity in the central soleal vein of a varicose vein patient with incompetent great saphenous veins (**A**). Serial examination with DUS revealed that the thrombus remained stable without any progression, 3 months after the first exam (**B**), and also in the postoperative period of the varicose vein surgery (**C**).

in one limb. Final examination of the postoperative DUS was performed 1–52 months after VV surgery (mean, 5.6 months). No patient presented complete thrombolysis of the IDDVT.

Case study

A 77-year-old female was referred to our vein center complaining of dullness in the left leg and bilateral calf vein bulging. She had a clinical history of cast immobilization in her right leg 10 years ago. She also had a history of lung cancer surgery 7 years ago, currently with no signs of recurrence. A DUS in the outpatient clinic showed that she had VVs due to incompetent GSVs in both legs. Preoperative DUS screening for DVT revealed that the right soleal vein had a linear-shaped thrombus with high echogeneity (**Fig. 1A**). The D-dimer value was 1.3 µg/mL, and she had no coagulation profile disorders. Three months after the initial diagnosis of the thrombus in the soleal vein, DUS showed that the thrombus had not changed in size or echogeneity (**Fig. 1B**). She completely understood the concept of IDDVT and gave written informed consent to undergo VV surgery involving high ligation of the right incompetent GSV. Compression therapy alone was performed on her left leg since the diameter of the left GSV was smaller (3 mm). Moreover, she had lumbar spinal canal stenosis, leading to severe symptoms in her left leg. She had no episodes of symptomatic DVT postoperatively. Furthermore, 20 months after VV surgery, DUS demonstrated that the thrombus in the right soleal vein had not changed in size or echogeneity (**Fig. 1C**).

Discussion

We aimed to clarify whether IDDVT in VV patients worsened after VV surgery (stripping or high ligation of the incompetent SV). We included patients who fulfilled the following criteria: (1) patients with VVs with incompetent SVs, (2) stability and clinical insignificance of IDDVT confirmed by serial DUS (we confirmed the IDDVT did not worsen in the preoperative period by serial DUS), (3) patients without risk factors for DVT (coagulation profile disorders, i.e., AT deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome) or malignancies, (4) VV surgery possible under local anesthesia (anesthesia not causing immobilization postoperatively), and (5) patients able to understand the concept of IDDVT. Among the VV patients with IDDVT detected by preoperative DUS, 28 patients with 30 affected limbs underwent VV surgery. Stable IDDVT that did not change in size or echogeneity in the preoperative period by serial DUS also remained stable and clinically insignificant in the postoperative course. Among the VV patients with IDDVT, one showed progression of IDDVT preoperatively. Physical and laboratory examinations with a high D-dimer value resulted in the detection of the preoperative progression of the IDDVT by DUS. The patient had decreased levels of protein S (64%; where 74–130% is the normal range).

Prevalence of IDDVT

We previously showed that 4.64% of VV patients had IDDVT.[1] Tamura and Nakahara assessed the performance of magnetic resonance venography and reported that it

revealed two cases of DVT (2.8%) in 72 VV patients.[6] Müller-Bühl et al. reported that there were 132 (5.6%) DVT cases among 2,357 VV patients in outpatient clinics.[7] Labropoulos et al. detected symptomatic distal DVT (not IDDVT) in 251 (4.8%) of 5,250 patients who were referred to the vascular laboratory clinic with suspicion of DVT.[4] Another study demonstrated that DUS screening for hospitalized patients detected 1.02% of isolated soleal and gastrocnemius vein thrombosis (141 cases among 13,759 hospitalized patients).[8] On the other hand, Hanzawa reported that DVT was detected in four out of 327 healthy volunteers (1.2%).[9]

Site of IDDVT

In this study, the majority IDDVTs were detected in the soleal veins (91%), followed by the peroneal, sural, and posterior tibial veins. Our previous report also showed that, in VV patients with STP, IDDVT was detected in the soleal vein alone.[1] Consistent with this, Singh et al. showed that the soleal vein was most commonly involved in IDDVT on initial DUS screening for DVT.[10] The second most common vein involved was the peroneal vein, and the least was the anterior tibial vein.

Recently, Ohgi S and Ohgi N investigated the characteristics of the isolated soleal vein thrombosis and its risk factors in 93 patients with symptomatic DVT in the soleal veins.[11] They demonstrated that: (1) the frequency of acute DVT was higher in the central and medial soleal veins than in other veins, (2) the isolated DVT in the central and medial soleal veins may result from the larger diameters of these veins compared with the others, as a local risk factor, and (3) in unilateral DVT cases, the frequency of DVT in the central soleal vein was higher than that in the medial soleal vein, and VVs may be involved as local factors. Our results concerning the site of IDDVT in patients with VVs (**Table 2**) are in line with these results. In addition, Ohgi et al. presented their data in the 34th Annual Meeting for Japanese Society of Phlebology (Okinawa, 2014), and showed that one cause of acute DVT in the soleal veins was VVs with incompetent GSV. Our results could not show a significant relationship between the site of IDDVT and the cause of VVs (incompetent GSV vs. SSV), or the site of IDDVT and the presence/absence of STP (chi-square for independent test, m×n contingency table, $p < 0.05$ as statistically significant).

Management of IDDVT

Optimal management of IDDVT remains controversial, given the absence of substantive evidence.[12] First, the guidelines in Japan ("Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (JCS 2009)") do not mention the management of IDDVT.[13] Second, "Antithrombotic

Therapy for VTE Disease: CHEST Guideline and Expert Panel Report" recommend serial DUS imaging of the deep veins for 2 weeks over anticoagulation in patients with acute isolated distal DVT without severe symptoms or risk factors for extension (Grade 2C).[12] Third, Schwarz et al. conducted a randomized controlled trial (RCT) to compare the efficacy and safety of a short-term course of anticoagulation therapy with compression therapy alone to treat patients with symptomatic, isolated distal DVT.[14] The primary endpoint of the study was progression of the distal DVT into the proximal deep veins and clinical pulmonary embolism. They concluded that patients with symptomatic distal DVT without ongoing risk factors do not benefit from short-term anticoagulation. Moreover, a review article entitled "The controversy of managing calf vein thrombosis" recommended that, in the absence of strong evidence to support anticoagulation over imaging surveillance with selective anticoagulation, observation and compression therapy with duplex surveillance remains a commonly practiced approach for the management of distal DVT.[15] On the contrary, Ro et al. conducted histopathological studies on venous thromboembolism and suggested that DVT in the calf, including DVT in the soleal veins, could proximally propagate, leading to secondary large thromboemboli as a cause of pulmonary thromboembolism (PTE).[16] Similarly, findings by Ohgi et al. suggested that calf DVT itself was an occasional embolic cause of PTE.[17] This discrepancy may be partly explained by the speculation that calf DVT in patients with PTE, especially fatal PTE, could be detected as remnant thrombi after the large thrombi in the DVT was degraded and the proximal part of the thrombus was released as an embolus. Further studies are clearly needed to clarify what type of calf DVT could be a risk for PTE.[1] In our center, we treat patients with IDDVT by elastic compression stockings (ECS) alone.[1] When patients have risk factors for DVT (coagulation profile disorders such as AT deficiency, protein C deficiency, protein S deficiency, and antiphospholipid syndrome, administration of procoagulatory medicines, such as hormone therapies, or malignancies, etc.), and the IDDVT is low-echogeneic, we use anticoagulation agents or antiplatelet agents.[1] "The Anticoagulation of Calf Thrombosis (ACT) Project" is currently underway to assess the benefits of therapeutic anticoagulation in the management of IDDVT.[18]

VV surgery for the patients with IDDVT

No consensus has been reached on whether or not indications for VV surgery include the presence of IDDVT.[1] A current Japanese guideline for treating VV patients with endovenous ablation lists patients with existing DVT (including IDDVT), or those with clinical history of DVT in the exclusion criteria.[5] On the other hand, in the Sym-

posium 2: "Venous thromboembolism as an adverse event of endovenous ablation surgery" held in the 35th Annual Meeting for Japanese Society of Phlebology (Nara, 2015), a chairperson mentioned that the presence of a solitary, old, linear-shaped IDDVT might not be the exclusion criteria for endovenous ablation surgery. Similarly, no consensus has been reached on whether or not indications for VV surgery involving high ligation of the junction between the SVs and deep veins with or without stripping, include the presence of IDDVT.[1] Raju et al. studied VV surgery in patients with DVT.[19] They performed high ligation of the saphenofemoral junction with stripping of the SVs in patients with deep vein obstruction and showed that it was tolerated in postthrombotic syndrome with compensated obstruction of the deep veins, although this is different in study design to ours. Kondo et al. also reported in the 34th Annual Meeting for Japanese Society of Phlebology (Okinawa, 2014) that five patients with IDDVT underwent VV surgery, including one case of stripping and four cases of endovenous laser surgery, and that IDDVT did not worsen in these patients.[20] Taken together, these results suggest that VV surgery is tolerated in VV patients with IDDVT, without IDDVT worsening, when there is careful selection of the patients for VV surgery, as well as perioperative management. Our criteria for VV surgery in patients with IDDVT include that the DVT was established (high-echogeneic) and its status did not change in the preoperative course for at least 3 months. Consistent with our criteria, Singh et al. also reported that all cases of propagation of isolated distal DVT and PTE were diagnosed within 3 months in the follow-up period.[10]

Limitations of the study and future direction

First, the sample size in our study was only 28 cases, thus a larger sample size is necessary. Second, a longer follow-up period is required to verify the changes to IDDVT. Third, this study was retrospective, and an RCT would ideally have been better. Fourth, to assess postoperative changes to IDDVT, patients were examined by DUS 1 month after VV surgery, based on the findings reported by Brittenden et al.[21] and van Rij et al.[22] On the other hand, Mii et al. reported that postoperative DVT occurred 3, 10, 26, and 42 days after stripping surgery in four out of 1,697 legs.[23] In addition, Wang et al. also reported that postoperative DVT occurred in 20 cases (5.17%) among 542 cases of stripping surgery in patients with GSV incompetence, and that 67.9% of the DVT cases were found within 2 weeks after the surgery.[24] These results highlight that it may not be possible to detect worsening of IDDVT if it happens 1–2 weeks after VV surgery. Therefore, this study did not completely clarify whether or not the IDDVT changed (or worsened) postoperatively. Instead, our results indicate that even if cases with worsened IDDVT 1–2 weeks after

VV surgery were included in our study, 1 month after the surgery, the status of the IDDVT returned to the same level as that in the preoperative period, suggesting that VV surgery was tolerated in patients with IDDVT. Examination by DUS 1 week after surgery might be useful for further assessment of IDDVT. Fifth, our study did not determine the reflux of the deep veins in patient with IDDVT. In a retrospective study, Saarinen et al. showed a significant association between popliteal reflux and stasis dermatitis in postthrombotic syndrome by symptomatic distal DVT.[25] Further study is warranted to clarify whether or not deep vein reflux was found by DUS in patients with IDDVT since its presence could be a useful index of worsening of IDDVT after VV surgery. Finally, direct oral anticoagulant (DOAC) is a new generation of DVT therapy.[26] Given that DOAC treatment of patients with symptomatic or asymptomatic distal DVT is expected, this might give us new information on a treatment strategy for VV patients with IDDVT.

Conclusion

Here, we conducted a retrospective clinical study to clarify whether IDDVT in VV patients worsened after VV surgery. We found that the central soleal vein was most commonly involved in IDDVT. Stripping or high ligation of the incompetent SV was performed as the VV surgery. Stable IDDVT did not change in size or echogeneity in the preoperative period, as determined by serial DUS, and also remained stable and clinically insignificant in the postoperative follow-up period (mean, 5.6 months). Our results suggest that VV surgery (stripping or high ligation of the incompetent SV) was tolerated in patients with stable IDDVT. Further studies are needed to clarify whether recurrence or propagation of IDDVT could occur in the long-term follow-up period.

Disclosure Statement

All authors in the study have no conflict of interest.

References

1) Shirasugi N, Horiguchi S, Shirato H, et al. Prevalence of isolated asymptomatic deep vein thrombosis in varicose vein patients with superficial thrombophlebitis: a single center experience in Japan. Ann Vasc Dis 2016; **9**: 2-7.
2) Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011; **53 Suppl**: 2S-48S.
3) Yamada N, Yamaki T, Iwata H, et al. The Japanese Vein Study: the survey of isolated calf deep vein thrombosis: The

Survey Committee of the Japanese Society of Phlebology. Jpn J Phlebol 2013; **24**: 211. (in Japanese)

4) Labropoulos N, Webb KM, Kang SS, et al. Patterns and distribution of isolated calf deep vein thrombosis. J Vasc Surg 1999; **30**: 787-93.

5) Satokawa H, Sugiyama S, Hirokawa, et al. Japanese guideline for endovenous treatment of varicose vein patients. Jpn J Phlebol 2010; **21**: 289-309. (in Japanese)

6) Tamura K and Nakahara H. MR venography for the assessment of deep vein thrombosis in lower extremities with varicose veins. Ann Vasc Dis 2014; **7**: 399-403.

7) Müller-Bühl U, Leutgeb R, Engeser P, et al. Varicose veins are a risk factor for deep venous thrombosis in general practice patients. Vasa 2012; **41**: 360-5.

8) Sales CM, Haq F, Bustami R, et al. Management of isolated soleal and gastrocnemius vein thrombosis. J Vasc Surg 2010; **52**: 1251-4.

9) Hanzawa K. Even in healthy general population, DVT was detected 1 out of 100 persons. Medical Technology 2007; **35**: 544-5. (in Japanese)

10) Singh K, Yakoub D, Giangola P, et al. Early follow-up and treatment recommendations for isolated calf deep venous thrombosis. J Vasc Surg 2012; **55**: 136-40.

11) Ohgi S and Ohgi N. Relationship between specific distributions of isolated soleal vein thrombosis and risk factors. Ann Vasc Dis 2014; **7**: 246-55.

12) Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. CHEST Guideline and Expert Panel Report. CHEST 2016; **149**: 315-52.

13) JCS Joint Working Group: Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (JCS 2009). http://www.j-circ.or.jp/guideline/pdf/JCS2009_andoh_h.pdf. (in Japanese)

14) Schwarz T, Buschmann L, Beyer J, et al. Therapy of isolated calf muscle vein thrombosis: a randomized, controlled study. J Vasc Surg 2010; **52**: 1246-50.

15) Masuda EM, Kistner RL, Musikasinthorn C, et al. The controversy of managing calf vein thrombosis. J Vasc Surg 2012; **55**: 550-61.

16) Ro A, Kageyama N, Tanifuji T, et al. Histopathological features about deep vein thrombosis resulting in fatal pulmonary thromboembolism from forensic autopsy. Jpn J Phlebol 2004; **15**: 365-9. (in Japanese)

17) Ohgi S, Tachibana M, Ikebuchi M, et al. Pulmonary embolism in patients with isolated soleal vein thrombosis. Angiology 1998; **49**: 759-64.

18) Horner D, Hogg K, Body R, et al. The anticoagulation of calf thrombosis (ACT) project: results from the randomized controlled external pilot trial. Chest 2014; **146**: 1468-77.

19) Raju S, Easterwood L, Fountain T, et al. Saphenectomy in the presence of chronic venous obstruction. Surgery 1998; **123**: 637-44.

20) Kondo Y, Muto S, Hirano H, et al. Varicose vein surgery in the patients with incidental distal deep vein thrombosis. Jpn J Phlebol 2014; **25**: 170. (in Japanese)

21) Brittenden J, Cotton SC, Elders A, et al. A randomized trial comparing treatments for varicose veins. N Engl J Med 2014; **371**: 1218-27.

22) van Rij AM, Chai J, Hill GB, et al. Incidence of deep vein thrombosis after varicose vein surgery. Br J Surg 2004; **91**: 1582-5.

23) Mii S, Eguchi D, Yamaoka T, et al. Deep venous thrombosis after stripping for primary varicose vein. Jpn J Phlebol 2004; **15**: 371-5. (in Japanese)

24) Wang H, Sun Z, Jiang W, et al. Postoperative prophylaxis of venous thromboembolism (VTE) in patients undergoing high ligation and stripping of the great saphenous vein (GSV). Vasc Med 2015; **20**: 117-21.

25) Saarinen JP, Domonyi K, Zeitlin R, et al. Postthrombotic syndrome after isolated calf deep venous thrombosis: the role of popliteal reflux. J Vasc Surg 2002; **36**: 959-64.

26) van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014; **124**: 1968-75.