Prevalence of Isolated Asymptomatic Deep Vein Thrombosis in Varicose Vein Patients with Superficial Thrombophlebitis: A Single Center Experience in Japan

Nozomu Shirasugi, MD, PhD,1 Sadaaki Horiguchi, MD, PhD,1 Hiroyuki Shirato, MD, PhD,1 Toshimitsu Kawakami, MD,1 Hisako Ono, AS,2 Shiho Yabuki, MD, PhD,1 Kumiko Jojima, MD, PhD,3 and Masanori Niimi, MD, DPhil3

Objective: Prevalence of asymptomatic deep vein thrombosis (DVT) in patients with primary varicose veins remains unclear.

Materials and Methods: Here, we conducted a retrospective study to clarify the incidence of asymptomatic DVT in patients with varicose veins, especially focusing on those with superficial thrombophlebitis (STP).

Results: Among 431 patients with primary varicose veins with saphenous vein incompetence, 20 (4.64%) had asymptomatic DVT. The presence of STP was a significant risk factor for asymptomatic DVT as 10 of the 24 (41.7%) patients with STP had asymptomatic DVT, and all cases having calf muscle vein thrombosis. In contrast, of the patients with primary varicose veins without STP only 2.46% had asymptomatic DVT.

Conclusions: In patients with primary varicose veins with STP, significant risk factors for DVT were being over C3 on the clinical, etiological, anatomical, and pathophysiological (CEAP) classification. (This article is a translation of Jpn J Phlebol 2014; 25: 13–19.)

Keywords: varicose veins, deep vein thrombosis, superficial thrombophlebitis

Introduction

Among several methods to investigate the venous system in the lower extremities, venography was the gold standard a couple of decades ago. Now, duplex ultrasound (DUS) has become the initial examination for imaging of the venous system.1) DUS is also performed to screen for deep vein thrombosis (DVT) before varicose vein surgery. Thus, the increasing number of cases with asymptomatic DVT has become recognized through the use of DUS for investigation of the venous system.2) However, the significance of asymptomatic DVT remains unclear. From the viewpoint of the present guidelines, sclerotherapy with polidocanol and endovenous ablation are defined as contraindicated treatments for patients with varicose veins, when DVT is detected, even though asymptomatic.3,4) Furthermore, management of asymptomatic DVT is controversial in patients who plan to have varicose vein surgery, i.e., there has been no consensus shown as to whether or not the indications for varicose vein surgery include the presence of asymptomatic DVT. Moreover, the frequency of DVT in Japanese patients with varicose veins has not been well documented.5) Here, we conducted a retrospective study to clarify the incidence of asymptomatic DVT in patients with varicose veins, especially focusing on those with superficial thrombophlebitis (STP).

Materials and Methods

We have included consecutively a total of 431 patients who were diagnosed with primary varicose veins due to saphenous vein incompetence, without any signs of DVT, at the outpatient clinic of our Varicose Vein Center from January 2010 to March 2011. Board certified vascular specialists diagnosed varicose veins. The patients underwent DUS for DVT screening, before varicose vein surgery, by a single clinical vascular technician using HI VISION Preirus (Hitachi Aloka Medical, Ltd., Tokyo, Japan). A local committee in our hospital approved the study protocol.

Among the 431 patients included in the study, 128 were male and 303 female. The mean age was 58.9 years (ranging from 22 to 84 years old), and 106 had varicose vein in the right leg, 124 in the left, and 201 in both.
Table 1 Incidence of DVT in varicose veins with/without STP

|               | DVT (+) | DVT (-) | Total no |
|---------------|---------|---------|----------|
| STP (+)       | 10 (41.7%) | 14       | 24       |
| STP (–)       | 10 (2.46%)  | 397      | 407      |
| Total no      | 20 (4.64%)  | 411      | 431      |

Shown as the number of cases. DVT: deep vein thrombosis; STP: superficial thrombophlebitis

Results

Among patients with varicose veins, 4.64% had DVT (Table 1)

Among the 431 patients with varicose veins due to saphenous vein incompetence, 20 (4.64%) had DVT.

The patients with STP had higher incidence of DVT (Table 1)

We also compared the incidence of DVT in patients who had STP at the initial presentation with that of patients with no STP. Among the 24 patients with STP, 10 had DVT (41.7%). In contrast, only 10 patients (2.46%) had DVT among the patients without STP. The incidence of DVT in patients with STP (41.6%) was significantly higher than that of the patients without STP (p <0.05 by chi-square test). The data suggest that presence of STP was one of the risk factors for concomitant DVT in the varicose vein patients.

DVT in the patients with STP was isolated calf DVT

Among those with STP, 10 patients with 12 lower limbs had DVT. Of these 10 patients, 2 were male and 8 female, with a mean age of 72.4 years (ranging from 63 to 80 year-old), and 2 patients had varicose veins in the right leg, 2 had varicose veins in the left leg, while 10 had varicose veins in both legs.

DVT was present in the same leg with STP. Two patients also had DVT in the opposite leg that had no STP. In all cases (12 limbs), the DVT was isolated calf DVT. All 12 limbs had soleal vein thrombosis, and among those, 3 limbs also had tibial vein thrombosis.

Among the 10 patients with DVT, none had a coagulation profile disorder (i.e., antithrombin deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome). None had pulmonary thromboembolism (PTE) examined by Chest computed tomography (CT) scan. Only one patient had a potential risk factor for thrombosis, that is, hormonal therapy for prostate cancer (chlormadinone acetate). Eight patients had an abnormal D-dimer value, although there was no significant difference between that in the patients with DVT (4.55 +/- 3.53 µg/ml) and that in the patients without DVT (1.37 +/- 2.31 µg/ml, p = 0.055 by unpaired Student t-test).

All patients with DVT showed C3 or more symptoms on the CEAP classification (Fig. 1)

All 10 patients with STP and concomitant DVT showed C3 or more symptoms on the CEAP classification. In contrast, among the 14 patients with STP who did not have DVT, only 4 patients showed C3 or more symptoms. These data suggest that clinical presentation with C3 or a more grade was one of the potential risk factors for concomitant DVT in the varicose vein patients with STP (p = 0.0005 by chi-square test).

There was no significant difference in diameter of the saphenous vein between the patients with DVT and those without DVT (Fig. 2)

We clarified whether the mean diameter of the incompetent saphenous veins correlated with the presence of DVT in the patients with STP. The mean diameter was measured at a point of 3–10 cm distal from the saphenofemoral junction (for great saphenous vein (GSV) incompetence) or at the point of the straight position of the short saphenous vein (SSV) below the popliteal fold, according to “The Guidelines for Endovenous Ablation in Patients with Varicose Veins in Japan.” The mean diameter of the incompetent saphenous vein was 8.29 +/- 2.74 mm in the patients with DVT, and 6.46 +/- 1.57 mm in those without DVT. There was no significant difference between the 2 groups (p = 0.05, by unpaired Student t-test).

Management of DVT

First, all patients with both STP and DVT were treated with elastic compression stockings (ECS). For STP, the patients were treated with low dose of aspirin (100 mg daily) for 2 weeks. Only 3 patients were treated with warfarin for DVT.
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...no one has reported any definite evidence showing that varicose veins cause DVT. Moreover, there has been no recent data on the incidence of DVT in varicose vein patients in Japan. Therefore, our data showing that among varicose vein patients, 4.64% had asymptomatic DVT is a novel and important result in Japan.

Can we consider the incidence of 4.64% higher than expected? Sakuma et al. reported the incidence of DVT and PTE in a large number of patients in Japan both in hospitals and outpatient clinics. They showed that the estimated incidence of DVT was 12 patients per 100000 people per year in Japan; i.e. 0.012% of overall patients both in hospitals and in outpatient clinics. Compared to that incidence, 0.012%, the incidence of asymptomatic DVT in varicose vein patients was higher.

Prevalence of asymptomatic DVT in varicose vein patients with STP

In our study, 41.7% of varicose vein patients with STP had asymptomatic DVT. Our result is congruent with those reported by an American group as well as the Japanese group. They showed 6 to 42% of patients with STP had DVT. These results suggest that STP was a predictive factor for occult DVT, leading us to conclude that varicose vein patients with STP should undergo DUS screening for occult DVT.

The exact mechanisms for occult DVT accompanied with STP remain undetermined. One could hypothesize that STP in varicose veins causes occult DVT, via the hypercoagulable states in local venous circulation due to the STP, or via the extension of thrombosis from the STP to the calf deep vein through direct perforators. Another hypothesis is that occult DVT first occurs due to venous stasis and that the DVT worsens venous stasis, leading to STP in the varicose veins. These possible mechanisms could not be distinguished in clinical situations even when we performed sequential DUS examination or venography for patients with STP. These two mechanisms are completely opposite. Thus, when treating varicose vein patients with STP and occult DVT, we should decide the management carefully in each respective case, especially weighing the pros and cons of an operation for varicose veins.

In our study, no patients with STP and DVT had a coagulation profile disorder (i.e., antithrombin deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome). On the other hand, Hanson et al. reported that, among patients with saphenous vein thrombosis and DVT, 35% of those had abnormal coagulation profiles, suggesting that examination of coagulation profiles is necessary in varicose vein patients with STP.

Discussion

Prevalence of asymptomatic DVT in varicose vein patients

One famous Japanese textbook for phlebology stated that varicose veins caused chronic venous insufficiency and were a possible risk factor for DVT. The Japanese Guideline for Prevention of Venous Thromboembolism also determined that varicose veins were one of the low-grade risk factors for venous thromboembolism (VTE). On the other hand, Kawasaki et al. mentioned in a review article for The Journal of Japanese Society on Thrombosis and Hemostasis that no one has reported any definite evidence showing that varicose veins cause DVT. Furthermore, “The Survey of Deep Vein Thrombosis and Venous Thromboembolism Prevention: Japanese Vein Study XIII” has not determined varicose veins as a risk factor for DVT. Additionally, the Japanese Guideline for Prevention of Venous Thromboembolism specified that the prevalence of DVT in varicose vein patients was “unknown”. Moreover, there has been no recent data on the incidence of DVT in varicose vein patients in Japan.
Management of STP in the varicose veins

As a treatment of STP in the varicose veins, we administered a low dose of aspirin (100 mg daily, Bayaspirin™) for 2 weeks as well as ECS. We use warfarin or heparin only in limited cases. In detail, we use warfarin for patients: 1) with fresh DVT in multiple calf veins, 2) with development of STP and/or DVT during initial treatment period, 3) with a coagulation profile disorder such as antithrombin deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome, and 4) with PTE. Wichers et al. also showed in their systematic review that active treatment with low-molecular-weight heparin (LMWH) or an non-steroidal anti-inflammatory drug (NSAID) could not demonstrate reduced incidence of VTE at longer follow-up.\(^\text{14}\) Taken together, more randomized controlled trials (RCT) are necessary before any evidence-based recommendation.

On the other hand, a Japanese group recommended an immediate operation for varicose veins with STP since they speculated that STP is one of the risk factors for DVT.\(^\text{15}\) We have performed elective surgery for varicose veins, after we treated the patients with STP by low-dose aspirin followed by DUS screening for DVT. Belcaro et al., from an English and Italian group, conducted an RCT study to evaluate the effects of several STP management plans on progression of the STP and the incidence of concomitant DVT at 3-months follow-up.\(^\text{16}\) They demonstrated that among several treatments: 1) ECS alone, 2) low dose subcutaneous heparin, 3) LMWH, 4) simple flush ligation of the saphenous vein, 5) stripping of affected veins, the incidence of STP extension was significantly higher in the group with 1) ECS, and 4) high ligation. They also showed that there was no significant difference in DVT incidence at 3-months follow-up among these treatment groups. Their results indicate that ECS and surgery, either simple flush ligation alone or stripping, have a similar treatment effect on the prevention of DVT in patients with STP. Therefore, elective surgery after treatment of STP, instead of immediate surgical treatment, could be one of the options for managing varicose vein patients with STP.

Management of asymptomatic DVT

In principle, we treat the patients with asymptomatic DVT by ECS alone. When the patients have risk factors for DVT (coagulation profile disorders such as antithrombin deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome, or administration of pro-coagulatory medicines such as hormonal ones, etc.), we use anti-coagulation agents (i.e., warfarin etc.) or anti-platelet agents. Schwarz et al. concluded from their RCT that patients with symptomatic, isolated calf muscle DVT did not benefit from anticoagulation by LMWH when compared with ECS.\(^\text{17}\) On the other hand, Ro et al. conducted histopathological studies on VTE and suggested that DVT in the calf, including DVT in the soleal veins, could play an important role in causing fatal PTE.\(^\text{18}\) They speculate that DVT in the calf and its proximal propagation could lead to secondary large thromboemboli, as a source for PTE.\(^\text{19}\) Moreover, data by Ohgi et al. suggest that calf DVT itself was an occasional embolic source for PTE.\(^\text{20}\) In our study, no PTE was found in the patients with STP or DVT. With ECS, no progression of asymptomatic DVT or PTE occurred in any patients during follow-up time. We speculate that not all DVT in the calf vein, but some calf DVT with unknown but certain characteristics (or risks), results in the development of thrombi to the proximal deep veins and PTE. Since a limitation of our study is that it is a retrospective study, further studies are needed to clarify what kind of calf DVT could be a risk for PTE. Ohgi et al. reported that the diameter of the soleal vein in the patients with PTE was more than 7 mm.\(^\text{20}\) We did not determine the diameter of the soleal vein in the patients with DVT.

Management of varicose veins with asymptomatic DVT: In the presence of DVT, is varicose vein surgery possible?

Management of varicose veins in the presence of asymptomatic DVT, in terms of surgery, remains controversial. A couple of decades ago, when venography was the gold standard for DVT screening, varicose vein surgery was contraindicated in patients with DVT. In our varicose vein center, on a trial basis, among the patients with asymptomatic DVT we carefully select the patients for varicose vein surgery using the requirements as follows; 1) sequential examination including DUS confirmed stability and clinical insignificance of asymptomatic DVT, 2) the patients do not have any risk factors for DVT such as a coagulation profile disorder including antithrombin deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome, 3) surgery is possible under local anesthesia alone, and 4) the patients can understand the concept of asymptomatic DVT and undergo the surgery on their own will and informed consent. One could hypothesize that varicose vein surgery benefits the patients if the varicose veins, especially STP, cause DVT. Another hypothesis could be that varicose vein surgery is contraindicated to patients with asymptomatic DVT from the viewpoint of induction of a hypercoagulable state by surgery. In other words, if the patients had unknown but certain factors to induce asymptomatic DVT, such factors could have induced STP in the varicose veins, and then could worsen the DVT in the perioperative period. The Japanese Vein Study: The 12th Survey of Varicose Veins by The Survey Committee of the Japanese Society of Phlebology showed that the incidence of symptomatic DVT in the postoperative course of patients with varicose vein surgery was 0.099%. Van Rij et al. found that postoperative DVT, either symptomatic or
asymptomatic, was detected in 5.3% of patients who had undergone varicose vein surgery.\textsuperscript{21} Given that varicose vein surgery is merely one of the options for the management of the benign disease, patients should be selected carefully for varicose vein surgery when they have asymptomatic DVT. Further study is needed to clarify what kind of patients with asymptomatic DVT could be suitable for varicose vein surgery.

Limitations and future direction

First, as evidence, our study did not show whether or not varicose vein surgery is possible in patients with asymptomatic DVT. Our ongoing trial may answer this question and we will report the results.

Second, in our study the incidence of asymptomatic DVT in varicose vein patients was 4.64%, which should be compared to that in healthy controls. However, little has been reported on the incidence in healthy controls. We do not have the data either. Although one famous Japanese textbook for phlebology stated that varicose veins were a possible risk factor for DVT,\textsuperscript{22} varicose veins were not an independent risk factor for DVT among outpatients with no recent trauma, surgery, or immobilization.\textsuperscript{23} Further study is necessary.

Third, our data suggest that STP was a risk factor for asymptomatic DVT in varicose vein patients. The finding is in line with the results earlier reported by others. On the other hand, even in the absence of STP, 2.46% of varicose vein patients had asymptomatic DVT. Few reports are available on the incidence and characteristics of DVT in varicose vein patients without STP. Studies to clarify these matters should be carried out.

Conclusion

We conducted a retrospective study to clarify the incidence of asymptomatic DVT in patients with varicose veins.
1) Among the 431 patients with varicose veins due to saphenous vein incompetence, 20 (4.64%) had DVT.
2) The presence of STP was one of the risk factors for concomitant DVT in varicose vein patients.
3) DVT in patients with STP was isolated calf DVT.
4) Clinical presentation with C3 or a more grade was one of the potential risk factors for concomitant DVT in varicose vein patients with STP.
5) Our results suggest that varicose vein patients with STP, and C3 or a more grade should undergo DUS screening for occult DVT, regardless of whether or not an operation for varicose veins is planned.

Disclosure Statement

All authors in the study have no conflict of interest.

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