Current aspects of diagnosis and treatment of superficial vein thrombosis of the leg

M. Stücker; S. Reich-Schupke

Venenzentrum der Dermatologischen und Gefäßchirurgischen Kliniken, Kliniken der Ruhr-Universität Bochum, Bochum

Keywords

Superficial venous thrombosis, heparin, compression, fondaparinux, rivaroxaban, duplex

Summary

The term „superficial venous thrombosis" (SVT) is more suitable to characterize the impact of the underlying disease instead of the old term „thrombophlebitis", since 25% of the patients have additional thrombembolic complications as a deep venous thrombosis or pulmonary embolism. If SVT is found in varicose veins, these veins should be therapied after the healing of the acute thrombosis. SVT independent of varicose veins are often seen in patients with malignancies, thrombophilia and other risk factors oft he deep vein thrombosis. Although the diagnosis of SVT could be made by clinical findings a creful duplex is essential to detect the extend of the thrombus and the exact location – perhaps with progress into the deep venous system. The complete venous system of both legs should be examined as the main reason for the SVT is hypercoagulability. Therefore, concomitant deep venous thrombosis can be detected on the same but also on the other leg. The therapy of SVT depends on the affected vein: 1) In small tributary veins cooling, compression therapy and nonsteroidal antiinflammatory drugs as well as a small inzision and expression of the thrombus are sufficient. 2) In SVT of saphenous veins and larger tributaries with a length of 5cm or more, anticoagulation in prophylactic dose for 4–6 weeks and compression treatment for 3 months is recommended. In patients with risk factors like cancer, autoimmune disease or SVT in non-varicose veins, thromboembolic complications are often seen after the end of the 6-weeks anticoagulation. In these patients special instructions are helpful. 3) A SVT nearby (<3cm) the crossing to the deep venous system or with extend into the deep venous system should be treated like a deep venous thrombosis.

Schlüsselwörter

Oberflächenthrombose, Heparin, Kompression, Fondaparinux, Rivaroxaban, Duplexsonografie

Zusammenfassung

Der derzeit aktuelle Terminus Oberflächenthrombose spiegelt besser als der alte Begriff Thrombophlebitis die Ernsthaftigkeit des Krankheitsbildes wider, welches bei etwa 25% der Patienten mit weitere thromboembolischen Komplikationen wie tiefen (Bein)Venenthrombosen und Lungenembolien einhergeht. Treten die Oberflächenthrombosen in Varizen auf, sollten diese nach Abheilung der akuten OVT saniert werden. Oberflächenthrombosen abseits der Varizen treten gehäuft bei malignen Grunderkrankungen, Thrombophilie und anderen Risikofaktoren der tiefen Beinvenenthrombose auf. Obwohl die Diagnose in der Regel klinisch gestellt werden kann, ist die Duplexsonographie unverzichtbar, um die Ausdehnung des Thrombus und ein mögliches Übergreifen des Thrombus in das tiefe Beinvenensystem zu erfassen. Dabei ist das komplette Venensystem beider Beine vollständig zu sonografieren, da der entscheidende Faktor für die Oberflächenthrombose die Hyperkoagulabilität ist und daher begleitende tiefe Venenthrombosen durchaus auch auf der Gegenseite auftreten können. Die Therapie der Oberflächenthrombose ist gestaffelt nach den betroffenen Gefäßen: 1) Bei kleinkalibrigen Aststhrombosen sind Kühlung, Kompressionstherapie, nicht steroidale Antiphlogistika sowie eine Stichinzision mit Thrombusexpression angezeigt. 2) Bei Oberflächenthrombosen der Saphenavenen und großkalibriger Varizenäste über 5cm Länge wird eine Antikoagulation in Prophylaxedosierung über 4–6 Wochen empfohlen, begleitet durch eine Kompressionstherapie über 3 Monate. Bei Risikofaktoren wie Krebsleiden, Autoimmunerkrankungen oder Befall nicht variköser Venen kommt es nicht selten erst nach Absetzen einer 6wöchigen Antikoagulation zu thromboembolischen Komplikationen, so dass bei diesen Patienten entsprechende Instruktionen sinnvoll sind. 3) Reicht der Thrombus näher als 3 cm an das tiefe Venensystem heran bzw. greift er auf die tiefen Venen über, wird wie bei einer tiefen Beinvenenthrombose therapiert.

Correspondence to:
Prof. Dr. Markus Stücker
Klinik für Dermatologie, Venerologie und Allergologie
der Ruhr-Universität Bochum
Katholisches Klinikum Bochum
Gudrunstraße 56, 44791 Bochum

Venenzentrum der dermatologischen und gefäßchirurgischen Kliniken
Kliniken der Ruhr-Universität Bochum
Hiltroper Landwehr 11–13, 44805 Bochum
Tel. +49 234/8792–377 od. –378, Fax –376
E-Mail: m.stuecker@klinikum-bochum.de

Aktuelle Aspekte der Diagnostik und Therapie der Oberflächenthrombose des Beines
Phlebologie 2018; 47: 329–333
https://doi.org/10.12687/phleb2434-6-2018
Received: 26. June 2018
Accepted: 28. June 2018

Thrombophlebitis/venous inflammation or superficial venous thrombosis?

For a long time, the term thrombophlebitis or venous inflammation was preferred in Germany to allow patients to distinguish it better from deep vein thrombosis (DVT). However, this view has changed both internationally and nationally and currently the term superficial vein thrombosis (SVT) is also favoured in Germany. This is because a meta-analysis of 21 studies with a total of 4358 patients on the prevalence of DVT and an analysis of 11 studies with 2484 patients on the prevalence of pulmonary embolism in patients with SVT showed the weighted mean prevalence of DVT at the time of superficial thrombosis to be 18.1% and that of pulmonary embolism to be 6.9% (1). It is not only because of the possible complications of other thromboembolic diseases, but also in respect of the correct treatment that the terms thrombophlebitis and venous inflammation should be avoided, since this can reduce the quite common, but contraindicated prescription of antibiotics. For example, a study in Great Britain found that about 20% of doctors still prescribed antibiotics to treat SVT (2).

Frequency of SVT

With an annual incidence of 0.64 per thousand, superficial thrombosis is a relatively common disease. This was demonstrated in a year-long prospective multicentre study in a region near St. Etienne in France between 2011 and 2012. The SVT recorded in this study was more frequent in women than in men and increased with age, independent of sex. In this study, there was again a high proportion of 24.6% of patients with a concurrent DVT, and 4.7% of patients had a pulmonary embolism (3).

The simultaneous occurrence of superficial thromboses and DVT or pulmonary embolism is consistently well documented in the literature. It is now interesting that there is an elevated risk of thromboembolic events also in the months and years after this disease. 3.4% of patients with SVT with no accompanying DVT at the time of first diagnosis go on to develop the latter subsequently (4). Compared with the general population, the risk in the first three months after SVT is increased 71.4-fold. Whilst the risk of DVT admittedly decreases in the following months and years, even 5 years after SVT it is still 5.1 times higher than in the comparator group. The risk of a pulmonary embolism after SVT is increased 45.4-fold in the first three months, and after 5 years it is still 2.9 times higher. These epidemiological data indicate that SVT and DVT or pulmonary embolism result from a common state of hypercoagulability. The significance of hypercoagulablity is also supported by the fact that in up to 10% of cases, DVT is found in the contralateral leg. The risk factors such as malignancies, surgical procedures, immobility and fractures are accordingly the same in SVT as in DVT.

Risk factors for DVT as a consequence of SVT

The following risk factors for further thromboembolic events in the period after the acute phase can be identified in patients with acute SVT:

- Previous thromboembolic events (DVT, pulmonary embolism, SVT)
- Positive family history of DVT
- SVT not in varicose veins but in normal veins (5)

Varicose veins as a risk factor for SVT

Varicose veins are a significant risk factor for SVT. The relevance of varicose veins is demonstrated, for example, in the high frequency of SVT recurrences in patients whose varicose veins remain untreated. This clinical experience was confirmed in a study in patients with a history of spontaneous SVT and varicose veins over a follow-up observation period averaging 55 months (6). During their primary phase of SVT, all the patients were treated with 2.5 mg fondaparinux daily for 45 days. Nevertheless, 13 of the monitored 57 patients suffered another episode of SVT during the follow-up period. It was interesting that, although all patients with recurrence showed a thrombophilia defect, there was no significant difference compared to the group of patients without SVT recurrence.

Heat is not an additional risk factor

One might think that since patients with varicose veins often complain of increasing swelling and heaviness of the legs during hot weather, then SVT would also occur more frequently in the summer months. However this could not be confirmed in a large analysis with 1395 patients and an observation period of 4.75 years (7).

D-dimer level increased in varicose veins

D-dimers as a prothrombotic marker and highly sensitive measure for endogenous fibrinolysis are increased in varicose veins even when there is no clinically manifest SVT. This was shown when D-dimer levels were compared in varicose veins and in the arm veins of the same patient. When blood samples were taken from a healthy arm vein and a varicose vein and a healthy vein in the calf in patients and healthy controls, the median D-dimer level in the varicose veins was significantly higher at 319 ng/ml than in the arm at 218 ng/ml (p=0.003) (8). In contrast, the D-dimer levels in the arm and in the leg in the healthy control group did not differ, with a median of 269 ng/ ml versus 262 ng/ml (p=0.361). In the patient group, the ratio of the calf and cubital blood D-dimer values (1.14) also differed significantly from the 0.96 of the control group (8).

Rare condition: penile Mondor's disease

Whilst – as previously discussed – the term SVT is generally preferable, in the case of Mondor's disease, use of the term thrombophlebitis is more justified. Mondor's disease was described in 1939, primarily for veins of the lateral thorax, thoraco-epigastric or upper epigastric region specifically

in women. Phlebitis of the penis as a part of a generalised phlebitis was first described in 1955 by Braun Falco. Isolated penile thrombophlebitis was then reported as penile Mondor's disease by Helm und Hodge in 1958 (9). Corresponding to the later description, penile Mondor's disease is actually less common than the thoracic Mondor's disease. The clinical picture in the penis is typically of a palpable, cord-like structure associated with erythema and tenderness. The aetiology of the disease is ultimately unclear. Very different risk factors have been mentioned, trauma in particular playing a significant role both in the thoracic and the penile forms of Mondor's disease (▶Table 1). Although a particularly pronounced inflammatory reaction compared to the size of the thrombus appears typical in Mondor's disease, a non-compressible vein is usually detected on duplex ultrasound (10).

Cannabis and SVT

Local factors such as varicose veins and systemic influences such as general hypercoagulability can favour the occurrence of SVT. The extent to which this can be affected by systemic factors was demonstrated in a cannabis smoker with migratory SVT (11). For more than 5 years, the 28-year-old otherwise healthy man suffered from recurrent painful SVT not only of both legs, but also of the feet, hands and groin. Risk factors such as thrombophilia, malignant underlying diseases or rheumatic disorders were excluded, and only after intensive questioning did it emerge that the patient – who had previously denied smoking any form of tobacco – regularly smoked cannabis. He did this either as a joint, prepared from cigar wraps in which the tobacco was replaced by cannabis, or also as a cannabis-tobacco mixture. He himself had the impression that his SVT occurred more frequently the more he smoked cannabis. He subsequently had phases of smoking pure cannabis in a water pipe, when the frequency and intensity of the periods of inflammation had decreased. Once this connection had been recognised, he then stopped smoking cannabis entirely for one year and was completely free of symptoms. New SVT only re-occurred once he resumed smoking cannabis. Although this relationship has only been described as a case report, it can be worth talking to a patient about possible cannabis consumption if the genesis of a migratory thrombophlebitis is otherwise unclear.

Tab. 1 Risk factors for penile Mondor's disease

- Excessive and long sexual activity
- Prolonged sexual abstinence
- Local or also more distant infections
- History of sexually transmissible diseases
- Use of intracavernous drug or vacuum
- Thrombophilia in the specific sense
- Inguinal hernia operations
- Orchidopexy
- Behcet's disease
- Bodybuilding exercises
- Pelvic tumours
- Paraneoplastic syndromes
- Intravenous drug misuse
- General tendency to form clots

Diagnosis of SVT

SVT can usually be diagnosed clinically. Nevertheless, duplex ultrasound is an essential aid to diagnosis, and the following points should be considered:

- Extent of the thrombus with origin and end
- Transition to a DVT
- Examination of both (!) legs, since DVT often occurs in the contralateral limb at the same time as SVT
- Thrombus length greater than 5 cm into the saphenous veins (indication for anticoagulation at a prophylactic dosage)
- Thrombus present in the region of the saphenofemoral junction less than 3 cm from the deep vein system (indication for anticoagulation at a therapeutic dosage)

If the SVT occurs in the absence of varicose veins, other risk factors should be explored. In particular, underlying malignancies or other risk factors for thromboembolic events should be considered (12). In addition, attention should be paid to current and historical signs of pulmonary embolism.

Treatment of SVT

The treatment of SVT is defined in the German AWMF Guideline "Diagnosis and treatment of venous thrombosis and pulmonary embolism" of 10.10.2015 (13). The basic approach is to check the indication for anticoagulation. If the thrombus shows transfascial extension, then the procedure for a venous thrombosis should be followed. Treatment of SVT depends on the type of vessel affected and the size and extent of the thrombus (▶Table 2).

SVT in a varicose vein should lead to the surgical removal of that vein. The rate of complications after initial conservative therapy and subsequent surgery in the symptom-free interval is lower than with an immediate operation during still existing florid SVT. If applicable, immediate surgical treatment of the SVT and the varicose vein can be considered if the thrombotic event is very recent. In addition to anticoagulation, the guideline recommends compression treatment until the symptoms

Tab. 2 Type of treatment for SVT

Affected vein	Treatment
Small-calibre branch varicosities/side branches	Cooling, compression therapy, non-steroidal anti-inflammatories if needed, stab incision with expression of thrombus
Great or small saphenous vein or large-calibre branch varicosities from a thrombus length of 5 cm	Fondaparinux at a prophylactic dosage (2.5 mg/ day s.c.) for at least 4 weeks + compression therapy for 3 months
Thrombus closer than 3 cm from a junctional valve to the deep vein system and/or extension into the deep vein system	Anticoagulation as for a DVT at a therapeutic dosage for at least 3 months + compression therapy for at least 6 months

have regressed – generally for three months.

How cost-effective is the current treatment of SVT?

The principles of treatment stated in the German guideline on thrombosis and pulmonary embolism are used internationally and are well-established. Nevertheless, there are critical discussions in relation to the recommendation for several weeks of anticoagulation at a prophylactic dosage for SVT of the saphenous veins. This recommendation is based on the CALISTO study which confirmed an advantage of 45 days treatment with fondaparinux compared with placebo. Corresponding to the importance and quality of the study, it is published prominently in the New England Journal of Medicine (14). However, critics have pointed out that even in the placebo group, there was only a very low rate of thrombosis and pulmonary embolism at merely 1.3%. This means that even without pharmacological treatment 98.7% of patients did not develop thrombosis or pulmonary embolism. Therefore, a better selection of patients who actually require treatment appears desirable (15).

Rivaroxaban in SVT

In the SURPRISE study, rivaroxaban at a daily dose of 10 mg was compared with fondaparinux at a daily dose of 2.5 mg for 45 days for the treatment of SVT in relation to the prevention of thromboembolic complications. To counter the accusation of the limited cost-effectiveness of the CALISTO study, the SURPRISE study required the patients to have an additional risk profile (16). Thus, only patients with at least one of the following risk factors could be included in the study: age over 65 years, male sex, a history of SVT or DVT or pulmonary embolism, current or history of cancer, autoimmune disorder or thrombosis of non-varicose veins. As in the CALISTO study, the duration of treatment was 45 days. Remarkably, unlike the CALISTO study, the major proportion of thromboembolic complications in the SURPRISE study occurred only after the 45 days of treatment had ended. Although all the patients in the SURPRISE study had at least one of the above-named risk factors, the number of thromboembolic complications did not increase as originally assumed. Contrary to expectations, thromboembolic events occurred not in 3% in the treatment group, but only in 1.8%, so the question has to be asked as to the reliability of the non-inferiority statistics. Ultimately, neither the number of thromboembolic events nor the number of non-major bleeds differed significantly, although thromboembolic events occurred in 3.32% of patients in the rivaroxaban group compared with 1.79% in the fondaparinux group and non-major bleeds were recorded in 2.54% of patients in the rivaroxaban group compared with only 0.43% in the fondaparinux group. The fact that more patients in the oral rivaroxaban group had to be excluded from the study because of incorrect application of the medication than in the fondaparinux group (rivaroxaban 10 exclusions, fondaparinux 2 exclusions) was also unexpected.

So what do the results of the SURPRISE study mean for routine practice?

Patients with the above-named risk factors have an increased risk of developing thromboembolic complications even after 45 days of anticoagulation at a prophylactic dosage. At present, it is unclear whether prolonging the prophylactic anticoagulation beyond 45 days or a switch from prophylactic to therapeutic anticoagulation would be worthwhile. As a minimum, the relationship between the form of administration and adherence should be investigated for the defined administration period of 4–6 weeks, since adherence in the SURPRISE study among the group with oral medication was worse than in the group with subcutaneous administration.

Time course and rate of recanalisation after SVT

Duplex ultrasound checks in SVT serve to demonstrate in particular a possible progression of the thrombus into the deep vein system or also merely an extension of thrombus length into the system of superficial veins. Patients often wish for such checks to determine whether recanalisation has already occurred, especially at the end of drug treatment after 4–6 weeks. It is important to know that in the first 6 weeks, the thrombus thickness and length measured by duplex ultrasound generally hardly change even under treatment. In contrast, the clinical signs of inflammation such as redness, pain and over-warming regularly regress within 6 weeks. A marked decrease in thrombus length and diameter is not demonstrated until the checks after 3 and 6 months (17). It therefore seems sensible to warn patients at the start of the investigation that a thrombotic (partial) occlusion of the affected vessel is likely even after 6 months. That does not mean that further pharmacological treatment is necessary.

Conflict of interests

The authors state that there is no conflict of interests.

Ethical guidelines

Preparation of the manuscript did not involve any studies on humans or animals.

References

1. Di Minno MN, Ambrosino P, Ambrosini F, Tremoli E, Di Minno G, Dentali F. Prevalence of deep vein thrombosis and pulmonary embolism in patients with superficial vein thrombosis: a systematic review and meta-analysis. J Thromb Haemost. 2016 May;14(5):964–72. doi: 10.1111/jth.13279. Epub 2016 Mar 15.
2. Dua A, Heller J, Patel B, Desai S. Variability in the Management of Superficial Venous Thrombophlebitis across Practitioners Based in North America and the Global Community. Thrombosis. 2014;2014:306018. doi: 10.1155/2014/306018. Epub 2014 Oct 12.
3. Frappé P, Buchmuller-Cordier A, Bertoletti L, Bonithon-Kopp C, Couzan S, Lafond P, Leizorovicz A, Merah A, Presles E, Preynat P, Tardy B, Décousus H; STEPH Study Group. Annual diagnosis rate of superficial vein thrombosis of the lower limbs: the STEPH community-based study. J Thromb Haemost 2014; 12(6): 831–838.
4. Cannegieter SC, Horváth-Puhó E, Schmidt M, Dekkers OM, Pedersen L, Vandenbroucke JP, Sørensen HT. Risk of venous and arterial thrombotic events in patients diagnosed with superficial vein thrombosis: a nationwide cohort study. Blood 2015; 125(2): 229–235
5. Cosmi B, Filippini M, Campana F, Avruscio G, Ghirarduzzi A, Bucherini E, Camporese G, Imber-

ti D, Legnani C, Palareti G; Risk factors for recurrent events in subjects with superficial vein thrombosis in the randomizes clinical trail SteFlux (Superficial Thromboembolism Fluxum). Thromb Res 2014; 133(2): 196–202.
6. Karathanos C, Spanos K, Saleptsis V, Tsezou A, Kyriakou D, Giannoukas AD. Recurrence of superficial vein thrombosis in patients with varicose veins. Phlebology 2015 Jul 16.
7. Frappé P, Bertoletti L, Presles E, Buchmuller-Cordier A, Merah A, Le Hello C, Peycelon D, Tardy B, Décousus H. Seasonal variation in the superficial vein thrombosis frequency. Thromb Res. 2015 Dec;136(6):1116–1119.
8. Lattimer CR, Kalodiki E, Geroulakos G, Syed D, Hoppensteadt D, Fareed J. d-Dimer Levels are Significantly Increased in Blood Taken From Varicose Veins Compared With Antecubital Blood From the Same Patient. Angiology 2015 Oct; 66(9): 882–888.
9. Kantarcı UH, Dirik A, Öztürk YE, Kiriş İ, Duymuş M. Doppler Ultrasound and Magnetic Resonance Imaging Findings of Penile Mondor's Disease: Case Report and Literature Review. Pol J Radiol. 2016 Feb 2;81:36–8. doi: 10.12659/PJR.895569. eCollection 2016
10. Marsaudon E, Legal C, Gayoux D, Weber O. La maladie de Mondor pénienne: une observation. Rev Med Interne (2016).
11. Lee C, Moll S. Migratory superficial thrombophlebitis in a cannabis smoker. Circulation 2014; 130(2): 214–215
12. Sándor T. [Superficial venous thrombosis. A state of art]. Orv Hetil. 2017 Jan;158(4):129–138.
13. AWMF Leitlinie: Diagnostik und Therapie der Venenthrombose und der Lungenembolie. Verabschiedet am 10. Oktober 2015.
14. Decousus H, Prandoni P, Mismetti P, Bauersachs RM, Boda Z, Brenner B, Laporte S, Matyas L, Middeldorp S, Sokurenko G, Leizorovicz A; CALISTO Study Group. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. N Engl J Med 2010 Sep 23; 363(13): 1222–1232.
15. Blondon M, Righini M, Bounameaux H, Veenstra DL. Fondaparinux for isolated superficial vein thrombosis of the legs: a cost-effectiveness analysis. Chest. 2012 Feb;141(2):321–329.
16. Beyer-Westendorf J, Schellong SM, Gerlach H, Rabe E, Weitz JI, Jersemann K, Sahin K, Bauersachs R; SURPRISE investigators. Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial. Lancet Haematol. 2017 Mar;4(3):e105-e113.
17. Spirkoska A, Jezovnik MK, Poredos P.Time Course and the Recanalization Rate of Superficial Vein Thrombosis Treated With Low-Molecular-Weight Heparin. Angiology. 2014 May 7. [Epub ahead of print]