REVIEW

Long-term Outcomes After Deep Vein Thrombosis: Postphlebitic Syndrome and Quality of Life

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In this review, we critically assess the literature on the incidence of postphlebitic syndrome, risk factors for its occurrence, available therapeutic options, and its effects on quality of life. As well, we describe available tools to measure postphlebitic syndrome. Recent prospective studies indicate that postphlebitic syndrome, a chronic, potentially disabling condition characterized by leg swelling, pain, venous ectasia, and skin induration, is established by 1 year after deep vein thrombosis (DVT) in 17% to 50% of patients. The only prospectively identified risk factor for its occurrence is recurrent ipsilateral DVT. In the sole randomized study available, daily use of elastic compression stockings after proximal DVT reduced the incidence of postphlebitic syndrome by 50%. Treatment options for established postphlebitic syndrome are limited, but include compression stockings and intermittent compressive therapy with an extremity pump for severe cases. To date, quality of life after DVT has received little attention in the literature. The recent development of the VEINES-QOL questionnaire, a validated venous-disease-specific measure of quality of life, should encourage researchers to include quality of life as a routine outcome measure after DVT. There is no criterion standard for the diagnosis of postphlebitic syndrome, but a validated clinical scoring system does exist. More research on postphlebitic syndrome is needed to enable us to provide DVT patients with comprehensive, evidence-based information regarding their long-term prognosis, to help quantify the prevalence and health care burden of postphlebitic syndrome, and by identifying predictors of poor outcome, to develop new preventive strategies in patients at risk of developing this condition.

KEY WORDS: **postphlebitic syndrome; deep vein thrombosis; quality of life; long-term outcome.**
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Deep vein thrombosis (DVT) is a serious disorder with an estimated annual incidence of 1 per 1,000 persons per year and a lifetime incidence of 2% to 5%.[1] Numerous studies over the past 10 to 15 years have addressed the diagnosis, prevention, and treatment of DVT. Most studies have focused on short-term outcomes such as mortality, recurrence of thromboembolism, and bleeding. The findings of these studies have had a major impact on the acute management of patients with DVT.

By contrast, long-term outcomes after DVT such as the postphlebitic syndrome have received little attention in the literature. Postphlebitic syndrome is a chronic condition characterized by leg swelling, pain, edema, venous ectasia, and skin induration. Studies have shown that it usually manifests itself within the first 2 years after an episode of DVT.[2,3] Severe postphlebitic syndrome can lead to intractable venous leg ulcers, which are painful, decrease mobility, and require ongoing medical and nursing care. Even in less extreme cases, the functional status of affected patients may be impaired. Few studies have prospectively assessed the long-term outcome of patients with DVT. Although some investigators have documented the incidence of postphlebitic syndrome in DVT patients, information is lacking on risk factors for this syndrome and its impact on quality of life. The paucity of data in this area has stemmed, at least in part, from a lack of validated measures to assess outcomes following DVT.

In this review, we critically assess the available literature on the incidence, diagnosis, risk factors, and management of the postphlebitic syndrome. We also review what is known regarding the impact of postphlebitic syndrome on quality of life, and the tools available to measure this impact.

METHODS

A computer search of the MEDLINE database from 1966 to 1999 was performed to identify English-language articles dealing with the incidence of postphlebitic syndrome, risk factors for its occurrence, therapeutic options, available tools to measure postphlebitic syndrome, and quality of life associated with venous disorders, including postphlebitic syndrome. Either the term *postphlebitic syndrome* or *postthrombotic syndrome* was combined with 1 or more of the following terms: *risk factors, cohort study, prognosis, treatment outcomes*, and *quality of life*.

In addition, the bibliographies of all relevant articles were reviewed to obtain additional references not identified by the MEDLINE search. Because of the limited data available on this topic, we retained all studies retrieved by our search for which study patients had previous objectively documented venous thrombosis, and for which the method of diagnosis of postphlebitic syndrome was adequately described and included patient symptoms. The studies retained are critiqued in this review.

RESULTS

Diagnosis of Postphlebitic Syndrome

Unfortunately, there is no "gold standard" test for the diagnosis of postphlebitic syndrome. Different authors have defined it by various associations of symptoms, clinical signs, and evidence of venous obstruction, high venous pressures, or valvular reflux on objective testing (e.g., ultrasonography and plethysmography). The correlation between clinical findings and objective tests is poor.[2,3] There exists one validated clinical scoring system for postphlebitic syndrome, developed by Villalta et al.,[4] which assigns a severity score of 0 (not present or minimal) to 3 (severe) for 5 symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and 6 signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression). A score of 5 to 14 on 2 consecutive visits 6 months apart indicates mild or moderate postphlebitic syndrome, and a score of 15 or more or the presence of a venous ulcer indicates severe postphlebitic syndrome. Interobserver agreement (κ) is high (0.80 for symptoms, 0.77 for signs, 0.78 for the total score, and 0.75 for the severity of postphlebitic syndrome). The area under the receiver operating characteristic (ROC) curve for the cutoff point of mild/moderate versus severe postphlebitic syndrome was 0.98 ± 0.016, indicating high sensitivity and specificity. This relatively simple-to-use scoring system has been used in 3 European studies.[5–7] To date, however, its utility as a tool for the routine monitoring of patient outcomes after DVT has not been assessed.

Incidence of Postphlebitic Syndrome After DVT

A limited number of studies have prospectively measured the incidence of postphlebitic syndrome after DVT, and these are not directly comparable because of differences in follow-up time, patient selection, and definition of postphlebitic syndrome. Strandness et al. followed 61 patients with confirmed DVT for a mean of 39 months and found that 67% of patients had pain or swelling in the involved leg, 23% had skin changes and 5% had ulcers.[2] Beyth et al. followed 124 patients 8 years after DVT and found that 42% of surviving patients had at least 1 symptom suggestive of postphlebitic syndrome; however, a clinical examination was not done to confirm the diagnosis.[8] These studies suggested that postphlebitic syndrome is a common occurrence after DVT. However, interim follow-up assessments to determine the timing of onset of postphlebitic syndrome after acute DVT were not performed.

Two important recent studies that addressed the issue of timing of onset of postphlebitic syndrome demonstrated that postphlebitic syndrome in most cases becomes established within 1 to 2 years after DVT. Prandoni et al. conducted a prospective study of 355 consecutive outpatients with a first episode of DVT who were followed biannually at a single diagnostic facility in Padua, Italy, for up to 8 years.[5] Few patients were lost to follow-up. The outcomes studied were recurrent DVT, postphlebitic syndrome, and death. Postphlebitic syndrome was diagnosed using the Villalta scoring system described earlier.[4] Overall, 84 patients (23.7%) developed postphlebitic syndrome, 30.2% of whom had severe manifestations. The cumulative incidence was 17.3% after 1 year and 22.8% after 2 years of follow-up. The incidence of postphlebitic syndrome increased gradually to 29.1% by 8 years. The cumulative incidence of postphlebitic syndrome in this study was lower than in previous studies, which might be explained in part by 4 factors. First, 15% of patients had calf or popliteal DVT alone, which, compared with proximal DVT, may be associated with a lower risk of postphlebitic syndrome. Second, elastic compression stockings, which appear to reduce the incidence of postphlebitic syndrome after DVT (see below), were used systematically. Third, a standardized instrument was used to diagnose postphlebitic syndrome; hence, nonspecific symptoms or signs that in prior studies might have been labeled as postphlebitic syndrome would be less likely to be attributed to postphlebitic syndrome. Finally, study-specific patient factors may have contributed to the lower incidence (e.g., at inception, all were outpatients and hence may have been younger and healthier, and none had recurrent DVT). Brandjes et al.[6] conducted a randomized trial of compression stockings (40 mm Hg pressure at the ankle) after proximal DVT in 194 patients, and also used the Villalta scoring system[4] to diagnose postphlebitic syndrome. Mild to moderate postphlebitic syndrome occurred within 12 months in 25% of patients in the stocking group compared with 50% of control patients; for severe postphlebitic syndrome, these figures were 10% and 20%, respectively.

Hence, from the best studies available, it appears that postphlebitic syndrome is established by 1 year after DVT in 17% to 50% of patients. Despite the long-held belief that it takes 5 to 10 years for postphlebitic syndrome to manifest, these 2 studies showed that most cases become clinically apparent within the first 1 to 2 years of the acute DVT.

Risk Factors for Postphlebitic Syndrome

Unfortunately, though much effort has gone into identifying factors that increase the risk of acute DVT, little is known about risk factors for postphlebitic syndrome

after DVT. There appears to be minimal correlation between the venographic severity (e.g., degree of occlusiveness) of the initial thrombus and subsequent development of postphlebitic syndrome.[5,9] There may be a relation between proximal sites of thrombosis and postphlebitic syndrome,[3] although other investigators have not found this association.[5,10] The use of thrombolytic therapy (local, catheter-directed, or systemic) to treat DVT, despite its efficacy in lysing fresh thrombi, has not been consistently shown to reduce the risk of subsequent postphlebitic syndrome.[11–13]

Prandoni et al. showed that recurrent ipsilateral DVT was a strong predictor of postphlebitic syndrome (hazard ratio 6.4), but other clinical features such as patient-physician delay, risk factors for thrombosis, family history, and deficiencies of protein C, protein S, and antithrombin 3 were not.[5] In this study, the more common thrombophilic disorders such as factor V Leiden and prothrombin gene mutations were not measured. Of interest, Munkvad and Jorgensen detected activated protein C resistance in 26% of 46 patients with venous leg ulcers, but only a quarter of such patients had a prior history of DVT.[14] This suggests that activated protein C resistance may increase the risk of venous ulceration, a serious manifestation of postphlebitic syndrome, independent of increasing the risk of recurrent DVT (a strong predictor in Prandoni's study).

Longer periods of warfarin anticoagulation might diminish the risk of postphlebitic syndrome compared with shorter treatments by reducing recurrent DVT.[15,16] This may be particularly true for idiopathic DVT (i.e., DVT occurring in the absence of known risk factors for thrombosis): a recent clinical trial of patients with a first episode of idiopathic thromboembolism was terminated early because of the finding that 3 months of anticoagulation was associated with a recurrence rate of 27.4% per patient-year, compared with only 1.3% per patient-year among patients receiving extended periods of anticoagulation.[17] In a randomized trial of patients with proximal DVT,[6] the use of custom fit, graduated elastic support stockings for at least 2 years was strongly protective against postphlebitic syndrome, resulting in a 50% reduction in risk.

Factors predictive of postphlebitic syndrome in retrospective studies have included age, female gender, hormone therapy, varicose veins, and abdominal surgery. However, for some of these "predictors," the temporality of the association is questionable (e.g., varicose veins, as prior DVT may lead to secondary varicose veins). In a retrospective study of young women assessed at least 1 year after DVT, body mass index greater than 22 kg/m^2 was associated with an almost 5-fold risk of developing postphlebitic syndrome.[18] To date, however, no study has documented that weight loss improves postphlebitic syndrome.

Hence, from the 2 available prospective studies[5,6] the only clearly identified risk factor for postphlebitic syndrome is recurrent DVT, and the only identified protective factor is use of elastic stockings. Of these 2 studies, only Prandoni's was specifically designed to prospectively assess risk factors for postphlebitic syndrome.

Management of Postphlebitic Syndrome

Prevention. Clearly the most definitive way to prevent postphlebitic syndrome is to prevent the incident DVT, i.e., primary prevention. Because ipsilateral recurrence appears to be an important risk factor for postphlebitic syndrome,[5] secondary prevention, i.e., preventing recurrence in patients who have already had DVT should be an important goal. Prevention of DVT recurrence is achieved by ensuring adequate duration of anticoagulation for the acute DVT and by offering thromboprophylaxis, when indicated, to patients who are not on long-term anticoagulation. Consensus guidelines on the optimal means of preventing and treating venous thromboembolism exist and are regularly updated.[19] However, it is not known how widely and consistently these guidelines are implemented by practicing physicians. Studies currently under way are evaluating the optimal duration and intensity of warfarin anticoagulation required to minimize recurrence in subgroups of DVT patients.[20] Research is also needed on the optimal dose, duration, and clinical indications for thromboprophylaxis in subgroups of DVT patients who are not maintained on indefinite anticoagulation, e.g., patients with inherited thrombophilia or with established postphlebitic syndrome.

As reviewed earlier, the daily use of elastic stockings for at least 2 years after acute DVT appears to be an effective means of preventing postphlebitic syndrome,[6] but it is probably underused in the clinical setting. It has not yet been established whether the benefits of elastic stockings continue with indefinite duration of use, whether certain subpopulations of DVT patients benefit from them more than others, and whether stocking types other than the custom-made, graded compression type used in Brandjes' study are also beneficial in preventing postphlebitic syndrome. Hence, until more data are available, efforts should be made to routinely prescribe that these stockings be worn daily for at least 2 years after DVT, and possibly indefinitely. The potential disadvantages of stockings include their cost (upward of $100 per pair), the difficulty some patients have in putting them on, and the warmth and discomfort that may be associated with wearing them in hot weather. Also, their use is contraindicated in the presence of arterial insufficiency because, via their compression effect, they may worsen claudication.

Treatment. Once the postphlebitic syndrome is established, treatment options are aimed toward limiting progression to ulcer with the use of graduated elastic compression stockings, which reduce venous hypertension and improve tissue microcirculation,[21,22] local care of established venous ulcers with topical dressings,[21] and the use of intermittent compression therapy with an extremity pump to improve symptoms in patients with severe postphlebitic syndrome. In 2 small studies of patients

with severe postphlebitic syndrome, intermittent compression extremity pumps provided sustained benefit in most patients without reported side effects.[23,24]

Quality of Life After DVT

Traditional measures of morbidity and mortality are limited in their ability to describe and quantify the impact of illness, particularly chronic illness, on patients' health and daily functioning. Quality of life, by defining health in broader terms than morbidity and mortality, is an important end point to study when considering prognosis after DVT.[25] Only 1 published study measured quality of life as a long-term outcome after DVT. Beyth et al. interviewed 52 patients from a cohort of 124 patients with DVT who survived for 6 to 8 years.[8] As measured by the 36-Item Short-Form Health Survey (SF-36), a generic quality-of-life measure, patients with symptoms of postphlebitic syndrome had poorer perceptions of their health, lower levels of physical functioning, and more severe role limitations due to physical health than asymptomatic patients. An earlier study of the long-term effects of iliofemoral DVT showed that among 21 patients followed for 10 or more years, 11 of 12 men were disabled and unable to maintain a steady job because of their leg symptoms, and 7 of 9 women were unable to perform household duties and required a homemaker.[26] Although quality of life was not measured using a standardized instrument, the results indicate that this severe form of DVT had a profound effect on patient functioning.

With regard to venous disease-specific measures of quality of life, existing questionnaires are limited by their narrow focus (e.g., restricted to patients with varicose veins[27] or ulcers[28,29]), inadequate evidence of reliability, validity, and responsiveness,[30–32] the lack of a generic quality-of-life component,[28,29,33,34] or their unavailability in a validated English and Canadian French version.[34,35] Recently, the VEINES-QOL questionnaire, a patient-based measure of quality of life specifically for use in the routine monitoring of outcomes in chronic venous disease was developed and validated. The VEINES-QOL is reliable, valid, and responsive in 4 languages, including English and Canadian French.[36] The VEINES-QOL questionnaire is administered together with the Medical Outcomes Study SF-36, the current "gold standard" generic measure of health-related quality of life.[37] The VEINES-QOL questionnaire can be completed by the patient in 10–15 minutes, and is thus practical for routine use. It is hoped that the availability of a venous-disease specific quality of life measure will encourage researchers to routinely include patient-based outcomes in studies evaluating the longterm effects of DVT.

CONCLUSIONS

DVT is a common condition that affects adults of all ages and has the potential to affect a patient's health for many years after its occurrence. Because of the lack of information on long-term outcomes after acute DVT, it is difficult for physicians to provide DVT patients with individualized information about prognosis. From the few prospective studies available, it appears that postphlebitic syndrome is established by 1 year after DVT in 17% to 50% of patients. In the sole prospective study specifically designed to assess risk factors for postphlebitic syndrome,[5] the only significant predictor identified was recurrent ipsilateral DVT. A single randomized trial showed that use of elastic stockings for at least 2 years after proximal DVT reduced the rate of postphlebitic syndrome by 50%.[6] Hence, until more data are available, physicians should prescribe compression stockings after DVT. Treatment options for established postphlebitic syndrome are limited, but include compression stockings and intermittent compressive therapy with an extremity pump. Quality of life after DVT has received virtually no attention in the literature, but the development of the VEINES-QOL, a patient-based measure of quality of life for use in chronic venous disorders, should encourage researchers to include quality of life as a routine outcome measure after DVT.

Further research is needed to evaluate long-term outcomes after DVT using validated instruments to diagnose postphlebitic syndrome and to measure disease-specific quality of life. The true incidence of postphlebitic syndrome in different subpopulations of DVT patients has not been adequately established. As yet, no data are available on potential predictors of postphlebitic syndrome such as socioeconomic status, ergonomic factors (e.g., percentage of time spent standing), type and frequency of exercise, severity of symptoms and signs at presentation, comorbidity (e.g., arteriopathy, congestive heart failure), time to reach adequate anticoagulation during the initial presentation, use of low molecular weight versus unfractionated heparin, presence of the genetic mutations associated with thrombophilia, and pattern of use and strength of elastic stockings. With regard to quality of life, several important questions need to be addressed: How does quality of life after DVT differ in patients with and those without postphlebitic syndrome? Does quality of life vary with duration of treatment, site, and extent of DVT, or other factors? How does quality of life among patients with postphlebitic syndrome compare with that of patients with other chronic diseases?

Addressing these issues will enable us to provide our DVT patients with comprehensive, evidence-based information regarding their long-term prognosis, will help to quantify the prevalence and health care burden of postphlebitic syndrome, and, by identifying predictors of poor outcome, could lead to new preventive strategies in patients at risk of developing this condition.

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