ORIGINAL INVESTIGATION

Prevention and Treatment of Postphlebitic Syndrome

Results of a 3-Part Study

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Background: The true incidence of postphlebitic syndrome (PPS) following proximal deep venous thrombosis (DVT) and the efficacy of graduated compression stockings in preventing and treating PPS are unknown.

Methods: A 3-part study of 202 patients evaluated 1 year after proximal DVT: 2 randomized placebo-controlled trials of stockings and 1 prospective cohort of untreated patients. Patients were evaluated for PPS, using a standardized questionnaire, and for venous valvular incompetence, using photoplethysmography and venous Doppler. They were enrolled in study 1 or study 2 if they did not have symptomatic PPS and did not have or had venous valvular incompetence, respectively, and into study 3 if they had symptomatic PPS. Study 1 patients were left untreated and followed up for development of PPS every 6 months for a mean of 55 months. Study 2 patients were randomized to a below-knee stocking (20-30 mm Hg) or a matched placebo stocking, and followed up for development of PPS every 6 months for a mean of 57 months. Study 3 patients were randomized to an active stocking (30-40 mm Hg) or a matched placebo stocking and followed up every 3 months for treatment failure, defined a priori.

Results: In study 1, 6 (5.0%) of 120 patients were categorized as treatment failures, a rate similar to placebo-treated study 2 patients ($P=.10$). In study 2, 0 (0%) of 24 active and 1 (4.3%) of 23 placebo-treated patients were categorized as treatment failures ($P=.49$). In study 3, 11 (61.1%) of 18 active and 10 (58.8%) of 17 placebo-treated patients were categorized as treatment failures ($P>.99$).

Conclusions: Most patients do not have PPS 1 year after proximal DVT, and do not require stockings. We failed to show a benefit of stockings in patients with PPS, but the small numbers preclude definitive conclusions.

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DEEP VEIN thrombosis (DVT) is a relatively common disease that can be associated with pulmonary embolism, an acute complication,[1] as well as the postphlebitic syndrome (PPS), a chronic complication.[2] Rapid identification of DVT and treatment with anticoagulants virtually eliminates the risk of pulmonary embolism.[1] However, prevention and treatment of the PPS, which consists of chronic pain and swelling and, occasionally, ulceration of the leg, are problematic because anticoagulant therapy alone might not be effective, and there are few well-designed clinical trials to provide guidelines.

Patients with acute DVT usually present with pain and swelling due to venous obstruction and inflammation caused by the thrombus. Once anticoagulant therapy is initiated, venous obstruction usually resolves over several months due to recanalization and development of collateral venous channels, leading to initial improvement in pain and swelling.[3-5] However, over time, it is believed that venous valvular incompetence, produced when thrombosed venous segments recanalize, can cause venous hypertension, which in turn can result in recurrence of pain and swelling; this is typical of the PPS.[2] It is probable that venous valvular incompetence precedes, and is a sine qua non for, the PPS, although not all patients with venous valvular incompetence become symptomatic.[6]

In general, 2 approaches have been used in the prevention and treatment of the PPS: thrombolytic therapy[6-10] and graduated compression stockings.[11-16] Thrombolytic therapy has the potential to prevent morbidity from the PPS by lysing thrombi, thereby relieving acute obstruction and preventing the venous valvular damage and the residual venous obstruction that cause venous hypertension. However, clinical trials have not clearly shown that thrombolytic therapy reduces the incidence of the PPS[6,10] and it is unsuitable in most patients either because of the risk (eg, postoperative patients) or because it is unlikely to be effective due to the thrombus age.

Graduated compression stockings are considered to be the mainstay of therapy for PPS and are often routinely applied to patients shortly after a diagnosis of DVT is made. By counteracting venous hyper-

PATIENTS AND METHODS

The study was approved by the institutional review board of the participating McMaster University–based hospitals, Hamilton. Informed consent was obtained from all patients after the study was explained.

INTERVENTION

Patients who had presented with a first episode of objectively confirmed proximal (involving the popliteal or more proximal vein) DVT to a McMaster University–affiliated hospital were screened for eligibility into the study 1 year after their DVT. Patients were subdivided into those who presented with suspected symptomatic DVT and those who had DVT found on routine venography after major orthopedic surgery. The latter group consisted primarily of subjects enrolled in 1 of several trials of DVT prophylaxis. The presence of 1 or more of the following excluded patients from the study: (1) previous graduated compression stocking therapy, (2) geographic inaccessibility, and (3) failure to provide informed consent. If eligible and consenting, patients were evaluated with a standardized questionnaire to determine if they had clinical evidence of PPS, and objective testing to determine if they had evidence of venous valvular incompetence. Depending on the findings, they were enrolled in 1 of 3 studies.

DEFINITION OF PPS

There is no uniformly accepted definition of PPS. Intermittent and reversible pain and swelling can be seen acutely with DVT and for weeks and even months afterward, particularly when the patient becomes mobile. Thus, we believed it was important to allow the early reversible symptoms to subside before labeling a patient as having PPS. Therefore, a priori, we used the following definition of PPS: chronic (>1 month in duration), typical (better after a night's sleep and leg elevation, worse at the end of the day and after prolonged standing or sitting), and pain and swelling of the leg(s) 6 months or more after a proximal DVT. Patients were categorized as having PPS only if they had both pain and swelling.

TESTS FOR VENOUS VALVULAR INCOMPETENCE

Patients with either abnormal photoplethysmography and/or venous Doppler findings were considered to have venous valvular incompetence.

PHOTOPLETHYSMOGRAPHY

Photoplethysmography is a noninvasive test of venous valvular function in which a shortened venous refilling time is used to diagnose venous valvular incompetence. Photoplethysmography was performed according to standard techniques.[17] Published reports,[17] including our own study,[18] suggest that a venous refilling time of less than 20 seconds is indicative of venous valvular incompetence and, therefore, this cutoff was used.

VENOUS DOPPLER

The detection of reflux in the common femoral, superficial femoral, popliteal and/or posterior tibial veins, is a reliable indication of valvular incompetence.[19] For this study, Doppler was performed according to previously described methods.[18]

STUDY FLOW

Figure 1 presents the study flow. Patients who did not meet the criteria for PPS were eligible for study 1 if they had normal photoplethysmography and Doppler findings and for study 2 if they had either abnormal photoplethysmography or Doppler findings. Patients who were symptomatic with PPS, regardless of the results of photoplethysmography and venous Doppler, were eligible for study 3.

Patients enrolled in study 1 were left untreated and followed up at 6-month intervals. At these times, they were asked about clinical evidence of PPS. Patients who developed symptoms of PPS were considered to be treatment failures.

Patients enrolled in study 1 were allocated in a randomized double-blind trial to either a below-knee graduated compression stocking with a pressure of 20 to 30 mm Hg or a matched placebo stocking with no hemodynamic effect (1 to 2 sizes too large). Only the leg(s) with abnormal test(s) results were treated. Follow-up was performed after 6 months when patients were asked about clinical evidence of PPS

tension, stockings have the potential to reduce or eliminate symptoms and to prevent venous ulceration. Theoretically, stockings might be useful at 2 stages in the course of the PPS. They could prevent or delay symptoms in asymptomatic patients with venous valvular incompetence and they could relieve symptoms and prevent progression of disease in symptomatic patients. One single, randomized controlled trial has suggested symptomatic improvement in patients treated with such stockings at the time of DVT.[16]

To test a management strategy to reduce morbidity from PPS and delineate the role of stockings in the prevention and treatment of PPS, we conducted a 3-part study. Patients were seen 1 year after proximal DVT and asked about symptoms of PPS and evaluated for venous valvular incompetence.

Thus, we carried out 2 randomized placebo-controlled trials and 1 cohort study, for which we had 3 primary objectives: (1) to determine in asymptomatic patients if the presence of normal valvular function predicts lack of subsequent morbidity from the PPS, without the need for stockings (study 1); (2) to determine if asymptomatic patients with objective evidence of venous valvular incompetence are predisposed to the development of PPS and, if so, whether therapy with graduated compression stockings prevents or delays the onset of PPS (study 2); and (3) to determine if therapy with graduated compression stockings in patients with PPS following DVT is effective in reducing symptoms (study 3).

RESULTS

The study began in July 1990 and the last patient completed follow-up in December 1999. During the study period, 384 patients were screened for eligibility and

(see definition above) and stocking compliance. Stockings were replaced at each 6-month follow-up. Patients who developed symptoms of PPS were considered to be treatment failures.

Patients enrolled in study 3 were allocated, in a randomized double-blind trial, to either a graduated compression stocking with a pressure of 30 to 40 mm Hg or a matched placebo stocking with no hemodynamic effect (1 to 2 sizes too large). Patients with symptoms in the calf only received a "below-knee" stocking, and those with thigh symptoms received a "thigh-length" stocking. Only the symptomatic leg(s) was treated. Prerandomization stratification for patients with calf symptoms vs those with symptoms above the knee was done to ensure balanced randomization. Patients were encouraged to wear the stockings as much as possible during waking hours. A baseline assessment was performed and then patients were seen every 3 months for the duration of the study. The stockings were replaced every 3 months.

Patients in study 3 were considered to be treatment failures under any of the following circumstances:

1. The patient felt that the pain and/or swelling did not improve or was worse after the first 3-month treatment interval—further defined as the patient answering a global rating questionnaire (**Figure 2**) that they were worse or about the same.
2. The patient experienced symptomatic deterioration during any 2 consecutive treatment intervals—further defined as the patient answering the global rating questionnaire that they were worse in 2 consecutive intervals.
3. The patient experienced marked symptomatic deterioration during any treatment interval—further defined as the patient answering question 1 of the global rating questionnaire that they were worse and question 2 with answers e, f, or g (ie, a good deal, a great deal, or very great deal worse, respectively).
4. Symptoms caused 5 or more days of work absenteeism or inability to perform housework during any 3-month interval.
5. The patient developed a venous ulcer.

AVOIDANCE OF BIAS AND CONTAMINATION

Blinding was maintained by removing labels from stockings and by having patients remove their stockings before their 3- to 6-month assessments. To avoid interviewer bias, patients in study 1 were instructed not to inform the interviewer that they were not using stockings.

STATISTICAL CONSIDERATIONS

Analysis

For study 1, the primary analysis was a description of the incidence of treatment failure (and the 95% confidence interval [CI]). A secondary analysis comprised a comparison of the proportions of treatment failures in study 1 patients with the placebo arm of study 2 patients. For both study 2 and study 3, the primary analysis was a comparison of the proportion of treatment failures in the 2 arms of the study.

The occurrence of symptoms was treated in the context of survival analysis and the treatment failure–free survival of the treatment groups was estimated by the Kaplan-Meier method[20] and compared by the Mantel-Haenszel[21] test. Patients who died or were otherwise lost to follow-up and had not developed PPS were considered as event-free up to the time of the last visit. Proportions were compared using the Fisher exact test. Odds ratios as well as proportions and their corresponding exact 95% CIs were calculated where indicated.

Sample Size

For study 1, we hypothesized that asymptomatic patients without venous valvular incompetence would have a risk of developing PPS of no more than 20% within 2 to 3 years. Using the placebo-treated patients in study 2 as the control group (treatment failure rate of 50% vs 20%) and accepting a 2-sided α of .05 and a β error of .2, we estimated requiring a sample size of 46 patients. For study 2, we hypothesized that patients without symptoms but with venous valvular incompetence 1 year after proximal DVT would have a risk of developing PPS (treatment failure) of approximately 50% within 2 to 3 years if left untreated and that active stockings would reduce this to approximately 20%. Therefore, allowing a 2-sided α of .05 and a β error of .2, we estimated requiring a sample size of 46 subjects per group. For study 3, we estimated that 50% of patients would be classified as treatment failures with the active stocking and that 90% would be treatment failures with the placebo stocking within 2 years. Accepting a 2-sided α of .05 and a β error of .2, the estimated sample size was 25 patients per group.

143 were excluded. The 3 most common reasons for exclusion were previous DVT (n=63), prior use of graduated compression stockings (n=53), and geographic inaccessibility (n=17). Of 241 potentially eligible patients, 39 refused consent and 202 were enrolled.

Because more than 200 patients had been recruited over a period of 9 years (we estimated we would need a total of 188 patients), we decided to perform an interim analysis despite the fact that the required sample sizes had not been achieved in studies 2 and 3. The analysis was performed by a blinded statistician (M.G.) to determine if it was futile or worth continuing the study; it was decided to terminate the study.

Of the 202 eligible consenting patients, 47 were allocated to study 2 (asymptomatic PPS, venous valvular incompetence), 120 were allocated to study 1 (asymptomatic PPS, no venous valvular incompetence), and 35 were allocated to study 3 (symptomatic PPS, regardless of venous valvular incompetence). The key demographic data for the patients in the 3 studies are shown in the **Table**.

Of the patients in study 1, 6 (5.0%; 95% CI, 1.9%-10.6%) were considered treatment failures. Of the patients in study 2, 0 (0%) of 24 treated with active stockings were considered treatment failures, compared with 1 (4.3%) of 23 treated with placebo stockings ($P=.49$). The difference in the treatment failure rate in study 1 and the placebo-treated patients in study 2 is not statistically significant ($P=.10$).

Overall, 7 of 167 patients in studies 1 and 2 were considered treatment failures. When interpreted collectively, this study suggests that most patients (83%) are asymptomatic 1 year after proximal DVT, and if they are

asymptomatic at this time, they have a very low incidence of subsequent PPS.

Of the patients in study 3, 11 (61.1%) of 18 treated with active stockings were considered treatment failures compared with 10 (58.8%) of 17 treated with placebo stockings ($P>.99$). The 95% CI on the observed difference of 2.3% in the rates of treatment failure is –29% to +34%, meaning we cannot exclude a true, absolute benefit of stockings of almost 30%.

Of the 110 patients who were known to have originally presented with symptomatic DVT, 30 (27%) had PPS at 1 year and were randomized into study 3. In contrast, of the 82 patients who were known to have originally presented with asymptomatic DVT (usually found on routine, predischarge venography after orthopedic surgery), 3 (4%) had PPS and were randomized into study 3. This difference in the incidence of PPS is statistically significant (odds ratio, 9.9; 95% CI, 2.7-43.0; $P<.001$).

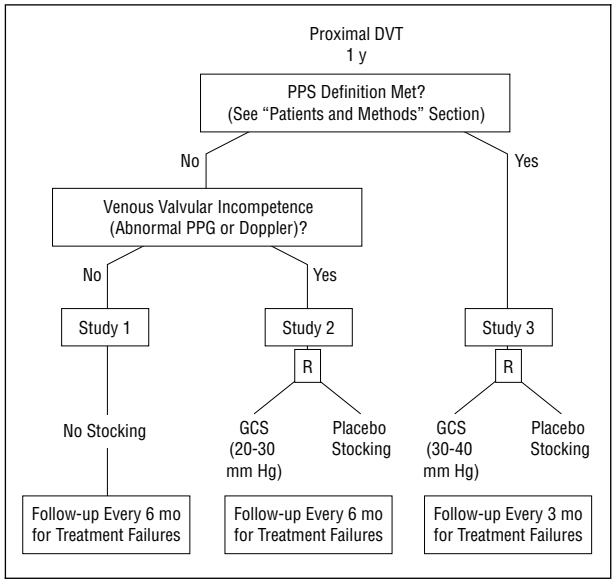

Figure 1. Study flowchart. DVT indicates deep venous thrombosis; PPG, photoplethysmography; R, randomize; and GCS, graduated compression stocking.

COMMENT

Based on the results of our studies, 3 important conclusions can be made. First, most patients (83%) do not have PPS 1 year after proximal DVT and they rarely develop it within 5 years or more after the diagnosis of DVT if they are asymptomatic at 1 year. Second, patients who develop asymptomatic DVT have a very low incidence of PPS (3/82=3.7%; 95% CI, 0.8%-10.3%) at 1 year. In contrast, patients with symptomatic DVT have a statistically and clinically significant increase in the incidence of PPS (30/110=27.3%; 95% CI, 18.9%-35.6%). Third, in all patients

Global Rating Questionnaire–Patient Response

Patient's Name: _____ Date: _____

1. In the last _____ , how have the patient's postphlebitic syndrome (pain and swelling) been compared with the previous _____ ?

   a) Worse
   b) About the same
   c) Better

   (If worse go to question 2)
   (If better go to question 3)

2. How much worse has the patient been?

   a) Almost the same, hardly any worse at all
   b) A little worse
   c) Somewhat worse
   d) Moderately worse
   e) A good deal worse
   f) A great deal worse
   g) A very great deal worse

3. How much better has the patient been?

   a) Almost the same, hardly any better at all
   b) A little better
   c) Somewhat better
   d) Moderately better
   e) A good deal better
   f) A great deal better
   g) A very great deal better

Figure 2. Global rating questionnaire.

Postphlebitic Syndrome Studies*

Characteristic	Study 1: Asymptomatic PPS, No VVI, No Stocking	Study 2: Asymptomatic PPS, VVI		Study 3: Symptomatic PPS			
				Active (30-40 mm Hg GCS)		Placebo Stocking	
		Active (20-30 mm Hg GCS)	Placebo Stocking	Calf	Thigh	Calf	Thigh
No. of patients	120	24	23	14	4	13	4
Age, mean (range), y	64.0 (25-91)	62.0 (33-78)	60.5 (24-87)	46.0 (18-79)	51.6 (28-74)	54.6 (22-75)	39.5 (25-64)
Sex, % female (No.)	56 (67)	42 (10)	48 (11)	50 (7)	50 (2)	62 (8)	100 (4)
Original DVT†							
Asymptomatic	67	7	5	1	0	2	0
Symptomatic	47	16	17	13	4	9	4
Unknown	6	1	1	0	0	2	0
Duration of follow-up, mean (range), mo	55.1 (0.2-99.2)	55.0 (2.0-97.3)	59.1 (18.3-97.2)	28.0 (2.9-62.4)	17.3 (3.0-56.6)	26.3 (2.8-73.8)	22.3 (2.7-44.2)
Deaths	17	3	0	1	0	0	0
Treatment failures (PPS)	6	0	1	8	3	7	3

*PPS indicates postphlebitic syndrome; VVI, venous valvular incompetence; GCS, graduated compression stocking; and DVT, deep venous thrombosis.
†Asymptomatic original DVT found on routine postoperative venography; symptomatic original DVT presented with symptoms suggestive of DVT.

who do not meet our criteria for PPS 1 year after proximal DVT, regardless of the presence or absence of venous valvular incompetence, stockings are not justified. This conclusion is based on the extremely low rate of development of PPS in the patients enrolled in studies 1 and 2 (7/167 = 4.2%; 95% CI, 1.7%-8.4%). We were unable to demonstrate a benefit of graduated compression stockings in patients with established PPS. Although this conclusion is limited by the relatively small numbers, the results do suggest that the benefit of stockings is limited.

Our study could be criticized because the use of "oversized" placebo stockings might have made some patients aware that they were being treated with a placebo. However, we excluded patients who had previously worn stockings, reducing the risk of unblinding. In addition, if patients were systematically unblinded we would have expected a bias in favor of preferring the "active" stocking and an increase in treatment failures in the placebo group, neither of which was seen.

Our results appear to conflict with a previous randomized trial in which patients with DVT were randomized (at the time of DVT) to either a stocking or no treatment.[16] However, that study differs in 2 ways from ours: first, no placebo was used that might have biased the assessment and, second, the definition of the PPS and treatment failures were different. In our study, we used a definition that focuses on lifestyle and quality of life, whereas in the previous study, a symptom score, which included asymptomatic findings that might lack clinical relevance, was generated based on signs as well as symptoms of PPS.

Based on our study results and clinical experience, we recommend the following strategy in patients with acute DVT. Empirically, to relieve acute pain and swelling, simple maneuvers, such as elevating the leg and avoiding aggravating positions and activities, should be strongly recommended. We advise against the routine use of stockings shortly after DVT except under unusual circumstances because they can be difficult to put on in symptomatic patients, they are likely to fit poorly once the acute swelling dissipates, and, in our experience, the acute symptoms resolve within 1 to 3 months after DVT. We limit stocking therapy to those with severe symptoms and tend to use "lightweight" stockings. We also believe waiting for 1 year is reasonable since none of our patients developed substantial symptomatic worsening and none developed severe sequelae, such as skin ulceration. If patients do not have symptomatic PPS at 1 year, stockings can be avoided and the patients reassured that their subsequent risk of symptomatic worsening is very low. In symptomatic patients with PPS, we recommend a trial of properly fitted graduated compression stockings since although we were unable to demonstrate a clear benefit, the study did not have enough power to detect a clinically important improvement in symptoms. In addition, our clinical experience, as well as a limited number of published studies, suggests that some symptomatic patients benefit from stockings. Finally, patients for whom stockings fail or who are intolerant of stockings, should undergo a trial of intermittent compression therapy with an extremity pump, which we have found beneficial in a significant proportion (approximately 75%) of patients.[22] We believe that the above minimizes expense and results in trivial morbidity. However, further large trials are required to determine if stockings are truly of benefit in symptomatic patients with PPS.

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