Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial

Susan R. Kahn MD MSc, Ian Shrier MD PhD, Stan Shapiro PhD, Adrielle H. Houweling MSc, Andrew M. Hirsch MD, Robert D. Reid PhD MBA, Clive Kearon MB PhD, Khalil Rabhi PhD, Marc A. Rodger MD MSc, Michael J. Kovacs MD, David R. Anderson MD, Philip S. Wells MD MSc

Abstract

Background: Exercise training may have the potential to improve post-thrombotic syndrome, a frequent, chronic complication of deep venous thrombosis. We conducted a randomized controlled two-centre pilot trial to assess the feasibility of a multicentre-based evaluation of a six-month exercise training program to treat post-thrombotic syndrome and to obtain preliminary data on the effectiveness of such a program.

Methods: Patients were randomized to receive exercise training (a six-month trainer-supervised program) or control treatment (an education session with monthly phone follow-ups). Levels of eligibility, consent, adherence and retention were used as indicators of study feasibility. Primary outcomes were change from baseline to six months in venous disease-specific quality of life (as measured using the Venous Insufficiency Epidemiological and Economic Study Quality of Life [VEINES-QOL] questionnaire) and severity of post-thrombotic syndrome (as measured by scores on the Villalta scale) in the exercise training group versus the control group, assessed by *t* tests. Secondary outcomes were change in generic quality of life (as measured using the Short-Form Health Survey-36 [SF-36] questionnaire), category of severity of post-thrombotic syndrome, leg strength, leg flexibility and time on treadmill.

Results: Of 95 patients with post-thrombotic syndrome, 69 were eligible, 43 consented and were randomized, and 39 completed the study. Exercise training was associated with improvement in VEINES-QOL scores (exercise training mean change 6.0, standard deviation [SD] 5.1 v. control mean change 1.4, SD 7.2; difference 4.6, 95% CI 0.54 to 8.7; $p = 0.027$) and improvement in scores on the Villalta scale (exercise training mean change –3.6, SD 3.7 v. control mean change –1.6, SD 4.3; difference –2.0, 95% CI –4.6 to 0.6; $p = 0.14$). Most secondary outcomes also showed greater improvement in the exercise training group.

Interpretation: Exercise training may improve post-thrombotic syndrome. It would be feasible to definitively evaluate exercise training as a treatment for post-thrombotic syndrome in a large multicentre trial. (Trial registered at www.controlled-trials.com, no. ISRCTN56430072.)

Competing interests: Please see end of article.

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Correspondence to: Dr. Susan R. Kahn, susan.kahn@mcgill.ca

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Chronic post-thrombotic syndrome develops in up to one-half of patients with deep venous thrombosis and is associated with varying combinations of leg pain, heaviness, swelling, edema, hyperpigmentation and varicose collateral veins. In severe instances, lipodermatosclerosis and venous ulcers occur.[1] Patients with post-thrombotic syndrome have substantially impaired quality of life.[2,3] Given that effective treatments are lacking, new approaches to managing post-thrombotic syndrome are needed.[4]

Exercise training is an effective treatment for arterial claudication[5,6] and may also improve post-thrombotic syndrome.[7] Potential mechanisms include improved endurance resulting from increased aerobic capacity, reduced muscular effort from improved strength, reduced swelling and discomfort via improved function of the calf muscle pump and improved musculoskeletal function via increased flexibility of ankle and knee joints.[8,9]

We performed a pilot trial to obtain data on the effectiveness of exercise training to treat post-thrombotic syndrome and to assess the feasibility of performing a multicentre study to address this question.

Methods

Setting and participants

Potential study participants were identified at two Canadian study sites via physician referral and posting of patient-directed recruitment fly-

ers. Potentially eligible patients were those aged 18–75 years with unilateral, symptomatic deep venous thrombosis objectively diagnosed at least six months previously and current ipsilateral manifestations in the leg consistent with post-thrombotic syndrome. Patients meeting these criteria were invited to a screening visit, where a trained research coordinator administered the Villalta scale for assessing post-thrombotic syndrome.[10] Those with a score of five or greater were classified as having post-thrombotic syndrome. Patients were ineligible if they had contraindications to exercise training (e.g., lower-extremity arthritis, angina, severe obstructive lung disease), had a life expectancy of less than six months, were pregnant or lactating, had an open venous leg ulcer, were not English- or French-speaking, were geographically inaccessible for follow-up visits, or were unwilling or unable to provide signed informed consent.

Before randomization, potentially eligible patients were given a physician-supervised exercise stress test using the modified Bruce ramp protocol.[11] Patients whose exercise test was stopped for reasons other than fatigue alone (e.g., severe dyspnea, chest pain, electrocardiographic coronary ischemia or arrhythmia) were excluded from the trial.[12] Written informed consent was obtained from all patients before participation in the study, and ethics approval was obtained from the Jewish General Hospital Research Ethics Board and the Ottawa Hospital Research Ethics Board.

Study protocol

Randomization and blinding

Patients were randomized to exercise training or control via a web-based program (Dacima Software Inc.) that ensured concealment of treatment allocation. Randomization was stratified by study centre. Each study site had two research assistants, one unblinded and one blinded to treatment allocation. The unblinded assistant notified patients of their allocated treatment only after the baseline assessment was completed, interacted with the exercise training facility to arrange appointments for exercise-training patients and administered the control treatment to control patients. The blinded assistant performed the baseline, three-month and six-month assessments of all patients, who were instructed not to reveal their allocated treatment.

Intervention and control treatments

The intervention was an exercise training program consisting of a six-month program with strengthening, stretching and aerobic components designed to improve leg strength, leg flexibility and overall cardiovascular fitness. Patients were asked to attend 15 one-on-one sessions with an exercise trainer (3 sessions per week in the first two weeks, 2 per week in the third week, 1 per week in the fourth week and 1 per month thereafter). The first three sessions lasted 60 minutes, and subsequent sessions lasted 45 minutes.

During the first session, patients were given an individualized exercise prescription and a supervised training session. Exercise prescriptions followed the guidelines of the American College of Sports Medicine for achieving and maintaining cardio-respiratory fitness (60–120 minutes per week of aerobic exercise performed to within 60%–85% of maximal heart rate).[13] Prescriptions were individualized based on results of the pre-randomization exercise stress test and the type of aerobic activity preferred (e.g., walking, jogging). Patients were instructed to do the strengthening program three to four times per week, the stretching program seven times per week and the aerobics program for 60–120 minutes per week. Each patient was given a digital heart-rate monitor to verify that he or she was training at the prescribed intensity level, and was asked to keep a daily log of frequency, duration and type of exercise performed.

In the second and subsequent sessions, the trainer provided support, addressed difficulties and gradually increased exercise intensity. After a few sessions, if the trainer judged that the patient understood the principles of modifying the program to ensure a training effect continued to be achieved, some face-to-face sessions were replaced by phone calls.

The control treatment was a standardized, one-hour educational slide presentation on post-thrombotic syndrome followed by phone calls at one, two, four and five months to inquire about general well-being and leg-related symptoms. It aimed to simulate the attention and contact received by exercise training patients. Control group patients were asked not to alter their usual level of physical activity during the study.

Wearing elastic compression stockings during exercise has neither harmful nor beneficial effects in patients with post-thrombotic syndrome.[14] We did not require patients to wear compression stockings during the trial; however, we documented their use.

Outcomes

Feasibility indicators

Criteria were established a priori as indicators of the feasibility of our study design (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.100248/DC1).

Effectiveness of intervention

The following outcomes were assessed in all patients at baseline and at the three- and six-month visits by the blinded study coordinator, who received standardized training on performing these measures:

Quality of life: Venous disease-specific quality of life (the primary outcome) was measured using the validated Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) questionnaire.[15] A difference of three points is considered clinically relevant.[15,16] Generic quality of life was measured using the Short-Form Health Survey-36 (SF-36) questionnaire,[17] which produces two (physical component and mental component) summary scores that reflect physical status and mental health status. A difference of four points is considered clinically relevant.[17] For both measures, lower scores indicate poorer quality of life.

Severity of post-thrombotic syndrome: The Villalta scale, a reliable and valid standard to measure post-thrombotic syndrome,[10,18] was used to grade the severity of post-thrombotic syndrome. This scale rates the intensity, from 0 to 3, of five venous symptoms and six signs. Points are summed into a total score. The Villalta scale yields a continuous score (the co-primary outcome; range 0–33) that can also be used to categorize the severity of post-thrombotic syndrome (none = a score of 0–4; mild = 5–9; moderate = 10–14; severe = ≥ 15 or presence of ulcer).[10]

Leg strength: Strength of the gastrocnemius–soleus calf muscle complex was measured with a Haberometer device (Michael Haber–Scientific Animation, Illustration and Webdesign, Montréal, Quebec), using a simple and reliable heel-lift test.[19] When the patient can no longer achieve the required heel-lift height or rate of lifting, the test is stopped and the total number of heel lifts performed is recorded.

Leg flexibility: Flexibility was assessed in the quadriceps, hamstring, gastrocnemius and soleus muscles with a handheld calibrated portable inclinometer (Saunders Group, Inc., Chaska, USA) using standard positions and manoeuvers.[20] According to the manufacturer, the instrument is accurate to ± 5º, or 10%. For each muscle group, a mean value (degrees) was recorded based on the average of three readings. For all measures, a larger angle indicates greater flexibility.

Time on treadmill: Exercise stress tests were performed before randomization and after completion of the six-month study intervention. A modified Bruce ramp protocol, designed for patients with low fitness levels, was used.[11,21] Time on treadmill (in minutes) was used as an estimate of exercise capacity.

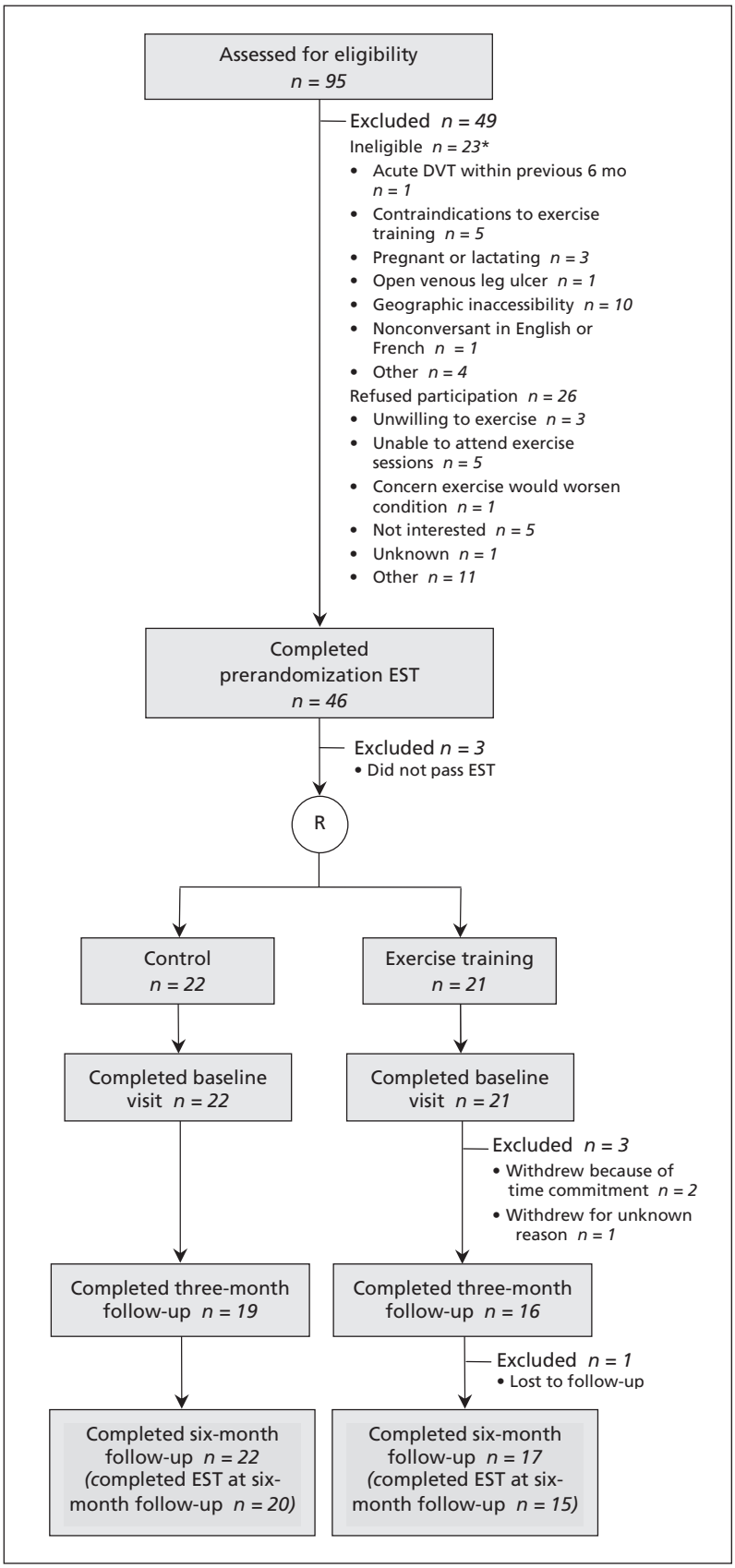

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow through the trial. DVT = deep venous thrombosis, EST = exercise stress test. *More than one reason could be marked off on the screening log.

Statistical analysis

Using a modified intent-to-treat analysis that included all participants with data at baseline and six months, we compared within-patient change from baseline to six months (mean, standard deviation [SD]) in the exercise training versus control groups in the following measures, using *t* tests: VEINES-QOL score, Villalta score, SF-36 physical and mental component scores, number of heel lifts, stretch angles for quadriceps, hamstring, gastrocnemius and soleus muscles, and time on treadmill. Subsequently, we used analysis of covariance to perform age- and sex-adjusted comparisons of the above measures, and we conducted linear regression analysis of the effect of treatment group (exercise training v. control) on change in VEINES-QOL score and in Villalta score, adjusted for baseline scores. Finally, we used χ^2 tests to compare change in category of severity of post-thrombotic syndrome over time in exercise training versus control groups.

In planned exploratory analyses, we performed repeated-measures analysis of variance (ANOVA) that included data from the three-month visit in addition to baseline and six-month data, and assessed the relation between change in VEINES-QOL score or Villalta score and change in leg strength, leg flexibility and time on treadmill.

Sample size

We aimed to generate effect sizes to aid with sample-size calculation for a larger, more definitive trial for which the likely primary outcome would be VEINES-QOL score. Based on practi-

Table 1: Baseline characteristics of study patients

Characteristic	Exercise training, no. (%)* n = 21	Control, no. (%)* n = 22	Characteristic	Exercise training, no. (%)* n = 21	Control, no. (%)* n = 22
Age, yr, mean (SD)	44.90 (11.34)	48.14 (10.65)	PTS severity category, no. (%)†		
Age group, no. (%)			Severe	4 (19.0)	1 (4.5)
< 40 yr	7 (33.3)	5 (22.7)	Most recent DVT was first DVT, no. (%)	16 (76.2)	16 (72.7)
40–65 yr	13 (61.9)	17 (77.3)	Time since most recent DVT, mo		
> 65 yr	1 (4.8)	0	Mean (SD)	39.9 (54.1)	38.1 (38.8)
Sex, male, no. (%)	11 (52.4)	8 (36.4)	Range	5.0–194.0	5.0–145.0
BMI, kg/m^2, mean (SD)	31.3 (7.6)	30.6 (6.1)	Side of DVT, no. (%)		
Level of education, no. (%)			Left	15 (71.4)	13 (59.1)
No school or grade school	1 (4.8)	1 (4.5)	Right	6 (28.6)	9 (40.9)
High school	2 (9.5)	2 (9.1)	DVT, highest segment affected, no. (%)‡		
College or university graduate	18 (85.7)	19 (86.4)	Iliac vein	3 (15.0)	3 (16.7)
Employment status, no. (%)			Common femoral vein	6 (30.0)	6 (33.3)
Full-time	14 (66.7)	17 (77.3)	Superficial femoral vein	3 (15.0)	4 (22.2)
Part-time	2 (9.5)	2 (9.1)	Popliteal vein	5 (25.0)	1 (5.6)
Not employed	5 (23.8)	3 (13.6)	Calf vein(s)	3 (15.0)	4 (22.2)
Comorbid conditions, no. (%)			VTE risk factors in most recent DVT, no. (%)		
Hypertension	3 (14.3)	5 (22.7)	Active cancer§ or chemotherapy	0	0
Diabetes	3 (14.3)	3 (13.6)	Pregnancy	1 (4.8)	2 (9.1)
Hyperlipidemia	4 (19.0)	2 (9.1)	Immobilization, trauma or surgery¶	6 (28.6)	9 (40.9)
Asthma	1 (4.8)	2 (9.1)	Hormone therapy (among women)¶	2 (20.0)	3 (21.4)
History of MI	0 (0.0)	1 (4.5)	IVC filter	0	1 (4.5)
Previous stroke	0 (0.0)	0 (0.0)	Factor V Leiden mutation, if known	5 (35.7)	4 (25.0)
Current smoker	4 (19.0)	1 (4.5)	Prothrombin gene mutation, if known	1 (7.1)	0
Severity of PTS and characteristics of prior DVT			Family history of DVT	7 (33.3)	9 (40.9)
PTS severity					
Villalta total score, mean (SD)	10.05 (4.44)	9.36 (4.47)			
Min–max	5.0–19.0	5.0 – 26.0			
PTS severity category, no. (%)†					
Mild	9 (42.9)	13 (59.1)			
Moderate	8 (38.1)	8 (36.4)			

Note: BMI = body mass index, DVT = deep venous thrombosis, IVC = inferior vena cava, MI = myocardial infarction, PTS = post-thrombotic syndrome, SD = standard deviation, VTE = venous thromboembolism.
*Unless otherwise indicated.
†Villalta scale categories of severity of post-thrombotic syndrome: mild = 5–9 points, moderate = 10–14 points, severe = ≥ 15 points.
‡Data on anatomical extent of previous DVT was missing for four patients in the control group and one patient in the exercise training group.
§Represents patients who had cancer diagnosed within the last six months, had metastatic cancer, were receiving ongoing treatment or were in palliative care.
¶Within three months before DVT.

cality and cost, we aimed to enroll 44 patients, which was expected to provide a 95% confidence interval (CI) half-width of about ± 2.4 points for change in VEINES-QOL scores, assuming an SD of this difference of four points.[16]

Results

Patient flow and baseline characteristics

From 2007 to 2008, 95 patients were screened, of whom 69 (73%) met the eligibility criteria for inclusion in the study (Figure 1). Of these, 43 (62%) consented to participate (21 randomized to exercise training, 22 to control). Three exercise training patients withdrew between baseline and three months (two because of time constraints and one for unknown reasons), and one was lost to follow-up after the three-month visit. There were no adverse events in either group.

Baseline characteristics of the study participants are shown in Table 1. Mean age was 47 years. Post-thrombotic syndrome was mild in 51.2%, moderate in 37.2% and severe in 11.6% of patients. The two groups were well balanced on post-thrombotic syndrome severity, but the exercise training group had a higher proportion of men and higher levels of self-reported habitual physical activity at baseline (shown in table of Appendix 1).

Adherence to allocated treatment

Detailed results related to adherence to allocated treatment by participants are reported in Appendix 1.

Effectiveness of exercise training intervention

The effectiveness of exercise training, expressed for each outcome as the difference in within-patient change from baseline to six months in exercise training patients versus control patients, is shown in Table 2. For the primary outcome, VEINES-QOL score, the mean difference in score from baseline to six months was 6.0 (SD 5.1) among exercise training patients versus 1.4 (SD 7.2) among control group patients, with a between-group difference of 4.6 points (95% CI 0.54 to 8.7, $p = 0.027$) in favour of exercise training.

For severity of post-thrombotic syndrome (the co-primary outcome), the mean difference in score from baseline to six months was –3.6 (SD 3.7) among exercise training patients versus –1.6 (SD 4.3) among control patients, with a between-group difference of –2.0 points (95% CI –4.6 to 0.6, $p = 0.14$) in favour of exercise training. Results in favour of exercise training were also obtained for between-group differences in the

Table 2: Comparison of change in study outcomes in exercise training group and control group patients from baseline to six months

Outcome (exercise training *n*; control *n*)	Exercise training group, mean (SD)			Control group, mean (SD)			Exercise training v. control group		
	Baseline	6 mo	Within-patient change	Baseline	6 mo	Within-patient change	Difference, within-patient change, exercise v. control, mean (95% CI)*	*p* value†	Age- and sex-adjusted *p* value,†
Quality of life									
VEINES–QOL score (18, 22)	46.4 (10.9)	52.4 (9.0)	6.0 (5.1)	48.4 (7.8)	49.8 (12.0)	1.4 (7.2)	+4.6 (0.54 to 8.7)	0.03	0.05
SF–36 PCS score	44.0 (9.1)	49.6 (7.8)	5.6 (7.7)	44.6 (8.6)	44.7 (10.7)	0.2 (7.6)	+5.4 (0.5 to 10.4)	0.03	0.09
SF–36 MCS score	50.9 (10.3)	51.6 (9.3)	0.8 (5.9)	49.8 (9.4)	50.2 (7.9)	0.4 (7.8)	+0.4 (–4.2 to 4.9)	0.87	0.68
PTS severity, Villalta score (18, 22)	10.6 (4.5)	7.0 (4.8)	–3.6 (3.7)	9.4 (4.5)	7.8 (5.8)	–1.6 (4.3)	–2.0 (–4.6 to 0.6)	0.14	0.12
Leg strength, heel lifts, (17, 22)	17.7 (19.2)	22.9 (16.1)	5.2 (10.6)	22.3 (13.9)	19.7 (7.5)	–2.5 (10.8)	+7.7 (0.7 to 14.7)	0.03	0.04
Leg flexibility, degrees (17, 22)									
Quadriceps	122.2 (14.2)	132.4 (19.4)	10.2 (20.5)	123.3 (17.0)	123.6 (16.9)	0.3 (6.6)	+9.9 (–1.0 to 20.7)	0.04	0.04
Hamstring	162.0 (16.0)	164.6 (18.3)	2.7 (11.0)	166.3 (18.1)	162.6 (19.8)	–3.7 (22.7)	+6.4 (–5.8 to 18.5)	0.29	0.47
Gastrocnemius	33.2 (10.0)	37.7 (9.5)	4.6 (8.0)	29.6 (5.9)	31.9 (6.4)	2.3 (8.9)	+2.2 (–3.4 to 7.8)	0.43	0.35
Soleus (16, 22)	37.7 (7.6)	41.0 (10.3)	3.3 (10.7)	35.9 (7.1)	38.5 (8.4)	2.6 (8.5)	+0.7 (–5.7 to 7.0)	0.83	0.88
Time on treadmill, min (15, 20)	10.5 (2.7)	10.0 (2.8)	–0.5 (2.08)	8.6 (2.1)	8.6 (2.1)	0.03 (1.05)	–0.53 (–1.76 to 0.69)	0.33	0.37

Note: CI = confidence interval, SD = standard deviation, PCS = physical component score, MCS = mental component score, PTS = post-thrombotic syndrome, SF–36 = Short-Form Health Survey-36, VEINES–QOL = Venous Insufficiency Epidemiological and Economic Study Quality of Life questionnaire.
*For all outcomes except Villalta score.
†*p* values are for the difference in change scores from baseline to six months between exercise and control patients using *t* tests (unadjusted) and ANCOVA (adjusted for age and sex). Positive change signifies improvement from baseline to six months. Analyses were done on patients with data at baseline and six months; three-month data were used in lieu of six-month data for one patient in the exercise training group who did not attend the six-month visit.

physical component score on the SF-36 (5.4 points, 95% CI 0.5 to 10.4, $p = 0.03$), leg strength (7.7 heel lifts, 95% CI 0.7 to 14.7, $p = 0.03$) and quadriceps flexibility (9.9 degrees, 95% CI –1.0 to 20.7, $p = 0.04$). Adjustment for age and sex gave similar results (Table 2). Hamstring and gastrocnemius flexibility also tended to improve more in the exercise training group, though not significantly. There was no difference between groups in change in time on treadmill.

Results were qualitatively similar when repeated-measures ANOVA incorporating data from the three-month visit was performed (data not shown) and when linear regression was performed (VEINES-QOL 4.23 points, 95% CI –0.06 to 8.64, $p = 0.034$; Villalta scale –1.82 points, 95% CI –4.56 to 0.94, $p = 0.18$). Finally, exercise training patients were more likely to show improvement in category of severity of post-thrombotic syndrome, with greater improvement seen at three months (exercise training 65% improved v. control 26%, $p = 0.021$) than at six months (exercise training 61% improved v. control 45%, $p = 0.32$).

With regard to potential mechanisms of the training effect, plots of change in VEINES-QOL score or Villalta score from baseline to six-month visit against change in number of heel lifts, flexibility of the various muscle groups or time on treadmill did not show any significant correlations (R^2 ranged from 0.003 to 0.086).

Use of elastic compression stockings was reported by 57.1% of patients in the exercise training group at baseline, by 42.9% at three months and by 52.4% at six months. Stocking use was reported by 72.7% of control group patients at baseline, 50% at three months and 68.2% at six months.

Interpretation

Results of our trial suggest that a six-month exercise training program designed to increase leg strength, leg flexibility and overall fitness may be an effective treatment for post-thrombotic syndrome, with improvement in many measures, particularly venous disease-specific quality of life and severity of post-thrombotic symptoms and signs.

Although the rate of patient dropout was low, all dropouts occurred in the exercise training group. An exercise program that requires less time with an exercise trainer and can be done independently at home or work may lead to better adherence. The design of our training program was drawn from studies of patients with arterial claudication, where maximal improvement occurred with sessions at least three times weekly for more than 30 minutes and continued for six months or longer.[6,7] In future studies involving patients with post-thrombotic syndrome, it would be worth investigating potential benefits of programs of shorter duration (e.g., three months) and evaluation of carryover or, conversely, washout effects once training is completed.

In exploring potential mechanisms for the effectiveness of exercise, we did not find associations between improvement in leg strength, leg flexibility or time on treadmill and improvement in VEINES-QOL score or severity of post-thrombotic syndrome. Mechanisms of improvement in the exercise group may not be attributable to increased exercise capacity, or the exercise group may have had improved individual anaerobic threshold that was not captured as a change in treadmill time. Perhaps the combined effect of increased leg strength and leg flexibility explains, at least in part, the improvement noted in the exercise training group. It is also possible that a physiologic effect was mediated through psychobiological (i.e., placebo) mechanisms.[22]

Our patients had post-thrombotic syndrome of varying severity and were likely representative of outpatients with this condition. We excluded patients older than 75 years because we were uncertain how well the exercise-based intervention would be tolerated. The average age of our participants was similar to that in other trials of interventions to treat post-thrombotic syndrome,[23,24] but it was about eight years younger than that of recent cohorts of unselected patients with deep venous thrombosis,[25,26] which suggests that younger patients with post-thrombotic syndrome may be more motivated than older patients to participate in treatment studies.

Two previous small trials assessed structured exercise programs in patients with venous disease. In the first, 72 patients with acute venous thrombosis were randomly assigned to daily walking plus physiotherapist-supervised exercise sessions, or to no exercise. At six months, vein recanalization, leg circumference and quality of life improved similarly in both groups.[27] Exercise was of lower frequency and duration than in our study, and adherence was not reported. In the second trial, 30 men with severe chronic venous insufficiency of diverse causes were randomly assigned to six months of exercise training (three months with supervision, then three months without supervision) or to no exercise. Exercise training improved calf muscle strength and pump function, but not valvular reflux, venous severity scores or quality of life.[28] Adherence to exercise in the second trial was similar to that in our study, but patients were older, only half had post-thrombotic syndrome and women were excluded; hence, it is difficult to compare its results with ours.

Limitations

The findings of our small trial should be interpreted with caution and require confirmation in a larger study.[29,30] Given that most of our patients were young, well-educated and active (Appendix 1), the results we obtained may not be generalizable to patients with post-thrombotic syndrome at other centres.

Conclusion

In this two-centre, randomized controlled trial of a six-month exercise training program involving patients with post-thrombotic syndrome, our trial design was shown to be feasible and our exercise training intervention achieved an effect that was clinically and statistically (for some outcomes) significant. These results provide the rationale to move forward with a larger, definitive trial of exercise training to treat post-thrombotic syndrome.

References

1. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med* 2004;164:17-26.
2. Kahn SR, Hirsch A, Shrier I. Effect of post-thrombotic syndrome on health-related quality of life after deep venous thrombosis. *Arch Intern Med* 2002;162:1144-8.
3. Kahn SR, Ducruet T, Lamping DL, et al. Prospective evaluation of health-related quality of life in patients with deep venous thrombosis. *Arch Intern Med* 2005;165:1173-8.
4. Kahn SR. How I treat postthrombotic syndrome. *Blood* 2009;114:4624-31.
5. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA* 1995;274:975-80.
6. McDermott MM, Ades P, Guralnik JM, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA* 2009;301:165-74.
7. Kahn SR, Shrier I, Kearon C. Physical activity in patients with deep venous thrombosis: A systematic review. *Thromb Res* 2008;122:763-73.
8. Araki CT, Back TL, Padberg FT, et al. The significance of calf muscle pump function in venous ulceration. *J Vasc Surg* 1994; 20:872-9.
9. Yang D, Vandongen YK, Stacey MC. Effect of exercise on calf muscle pump function in patients with chronic venous disease. *Br J Surg* 1999;86:338-41.
10. Kahn SR, Partsch H, Vedantham S, et al. Definition of postthrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost* 2009; 7:879-83.
11. Kaminsky LA, Whaley MH. Evaluation of a new standardized ramp protocol: the BSU/Bruce Ramp protocol. *J Cardiopulm Rehabil* 1998;18:438-44.
12. Darrow MD. Ordering and understanding the exercise stress test. *Am Fam Physician* 1999;59:401-10.
13. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc* 1998;30:975-91.
14. Kahn SR, Azoulay L, Hirsch A, et al. Effect of graduated elastic compression stockings on leg symptoms and signs during exercise in patients with deep venous thrombosis: a randomized cross-over trial. *J Thromb Haemost* 2003;1:494-9.
15. Lamping DL, Schroter S, Kurz X, et al. Evaluating outcomes in chronic venous disorders of the leg: Development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. *J Vasc Surg* 2003;37:410-9.
16. Kahn SR, Lamping DL, Ducruet T, et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. *J Clin Epidemiol* 2006;59:1049-56.
17. Ware JE, Kosinski M, Keller S. *SF-36 physical and mental summary measures: A user's manual*. Boston (MA): The Health Institute, New England Medical Center; 1994.
18. Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. *J Thromb Haemost* 2009;7:884-8.
19. Haber M, Golan E, Azoulay L, et al. Reliability of a device measuring triceps surae muscle fatigability. *Br J Sports Med* 2004;38:163-7.
20. Ekstrand J, Wiktorsson M, Oberg B, et al. Lower extremity goniometric measurements: a study to determine their reliability. *Arch Phys Med Rehabil* 1982;63:171-5.
21. Will PM, Walter JD. Exercise testing: improving performance with a ramped Bruce protocol. *Am Heart J* 1999;138:1033-7.
22. Crum AJ, Langer EJ. Mind-set matters: exercise and the placebo effect. *Psychol Sci* 2007;18:165-71.
23. O'Donnell MJ, McRae S, Kahn SR, et al. Evaluation of a venous-return assist device to treat severe post-thrombotic syndrome (VENOPTS): A randomized controlled trial. *Thromb Haemost* 2008;99:623-9.
24. Ginsberg JS, Hirsh J, Julian J, et al. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. *Arch Intern Med* 2001;161:2105-9.
25. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008;149:698-707.
26. Tick LW, Kramer MH, Rosendaal FR, et al. Risk factors for postthrombotic syndrome in patients with a first deep venous thrombosis. *J Thromb Haemost* 2008;6:2075-81.
27. Isma N, Johanssson E, Bjork A, et al. Does supervised exercise after deep venous thrombosis improve recanalization of occluded vein segments? A randomized study. *J Thromb Thrombolysis* 2007;23:25-30.
28. Padberg FT Jr, Johnston MV, Sisto SA. Structured exercise improves calf muscle pump function in chronic venous insufficiency: a randomized trial. *J Vasc Surg* 2004;39:79-87.
29. Arnold DM, Burns KE, Adhikari NK, et al. The design and interpretation of pilot trials in clinical research in critical care. *Crit Care Med* 2009;37:S69-74.
30. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004;10:307-12.

Competing interests: Susan Kahn is principal investigator of an ongoing trial funded by the Canadian Institutes for Health Research (CIHR) investigating active versus placebo compression stockings to prevent post-thrombotic syndrome after deep venous thrombosis, for which Sigvaris Corp. has provided active and placebo compression stockings. She is a coapplicant and steering committee member on an NIH-funded trial (funded by the United States National Institutes of Health) of pharmacomechanical catheter-directed thrombolysis plus standard anticoagulation alone. She has received honoraria to speak on post-thrombotic syndrome at various national and international academic conferences. Clive Kearon is principal investigator for a CIHR grant for the evaluation of a D-dimer-based management strategy for selecting patients with unprovoked venous thromboembolism for indefinite anticoagulation. He is a steering committee member for one recently completed and two ongoing studies of venous thromboembolism treatment by Boehringer Ingelheim. Marc Rodger served on an advisory board for Boehringer Ingelheim, Sanofi-Aventis and bioMérieux. He is appointed at the Ottawa Hospital Research Institute, which received compensation from Boehringer Ingelheim, Sanofi-Aventis, bioMérieux and LEO Pharma for this service. No competing interests declared by Ian Shrier, Stan Shapiro, Adrielle Houweling, Andrew Hirsch, Robert Reid, Khalil Rabhi, Michael Kovacs, David Anderson and Philip Wells.

Affiliations: From the Department of Medicine (Kahn, Hirsch) and the Department of Epidemiology and Biostatistics (Shapiro), McGill University; the Centre for Clinical Epidemiology and Community Studies (Kahn, Shrier, Shapiro, Houweling) Jewish General Hospital; and the Department of Chest Medicine (Rabhi), Hôpital du Sacré-Coeur de Montréal, Montréal, Que.; Minto Prevention and Rehabilitation Centre (Reid), University of Ottawa Heart Institute; the Departments of Medicine and Department of

Epidemiology and Community Medicine (Rodger, Wells), University of Ottawa, Ottawa, Ont.; the Department of Medicine (Kearon), McMaster University, Hamilton, Ont.; the Department of Medicine (Kovacs), University of Western Ontario, London, Ont.; and the Department of Medicine (Anderson), Dalhousie University, Halifax, NS

Contributors: Susan Kahn, Ian Shrier and Clive Kearon were responsible for the conception and design of the study. Stan Shapiro, Andrew Hirsch, Robert Reid, Marc Rodger, Michael Kovacs, David Anderson and Philip Wells were involved in the design of the study. Susan Kahn, Andrew Hirsch, Adrielle Houweling, Robert Reid, Marc Rodger and Philip Wells acquired the data. Susan Kahn, Adrielle Houweling, Khalil Rabhi, Ian Shrier and Stan Shapiro analyzed the data. Susan Kahn, Ian Shrier, Stan Shapiro and Adrielle Houweling interpreted the data. Susan Kahn and Adrielle Houweling drafted the manuscript. All of the authors critically revised the manuscript for important intellectual content, and all of them approved the final version submitted for publication. Susan Kahn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Editor's note: For the study protocol pertaining to this article, please see Appendix 2 (available at www.cmaj.ca/cgi/content/full/cmaj.100248/DC1).