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Does supervised exercise after deep venous thrombosis improve recanalization of occluded vein segments? A randomized study.

Short running title: Supervised exercise and DVT

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Summary

Objectives:

The aim of the present study was to evaluate weather early supervised exercise improves recanalization of acute deep vein thrombosis and reduces symptoms.

Patients and Methods:

From September 2001 to March 2004, 72 consecutive patients mean age 54±14 years, 39 (52%) men with deep vein thrombosis (DVT) proven with phlebography were randomized to: an exercise group (n=36) receiving routine anticoagulation, class II compression stockings and additionally supervised exercise and a control group (n=36) receiving the same therapy but no exercise. Patients were followed-up during six months. Phlebography was scored initially and at six-months.

Results:

There were at inclusion no differences between the two groups regarding age, body weight, BMI, calf circumference of the affected leg, and overall quality of life estimated by VAS-scale. In both groups there were significant reductions regarding calf circumference in the affected leg compared to the inclusion time, both at one-month (p=0.0012) and six month (p=0.0002) follow-up. The degree of recanalization of the affected venous segments was high and did not differ between groups. There were no recurrent DVT or pulmonary emboli or other treatment complications in any individual during the six-month follow-up period.

Conclusions:

Early exercise did not acutely exacerbate the risk of complications in patients with DVT. No benefits of early exercise were seen regarding the degree of recanalization of the thrombi, or faster resolution of pain or swelling. Nevertheless, our study shows that early exercise/ambulation is safe in combination with anticoagulation and compression stockings for

the majority of patients with DVT.

Key words:

DVT, exercise/ambulation, outpatient management, recanalization, thrombosis

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INTRODUCTION

Deep venous thrombosis (DVT) is a common disease occuring in approximately 1-2 cases per 1.000 individuals yearly [1, 2]. In spite of this high frequency surprisingly little is known about the positive and/or negative effects of exercise in patients with DVT. Not so long ago the need of prolonged bed-rest was considered essential for the treatment of DVT to control thrombotic propagation and reduce of the risk of pulmonary embolism (PE). Initial bed-rest is still a part of DVT treatment at many centres [3]. However, this treatment strategy in DVT has been critically questioned [4-8]. Additionally randomized studies have shown that the incidence of scintigraphically detectable PE is not reduced by bed-rest in the treatment of DVT [4, 7]. Instead bed-rest has been shown to promote thrombus progression [8-10]. Early mobilization in patients with DVT on the other hand does not increase the rate of PE or the complication rate [11], but instead reduces thrombus progression [8]. Why do we then have greater fear of dislodging clots by ambulation then the consideration of the risk for DVT progression and more severe post thrombotic sequele by avoiding activation and increasing venous flow?

Regression of on acute DVT is a slow process that continues for at least 9 months. It appears to be primarily mediated by enhancement of the endogenous fibrinolytic system, and increased tissue plasminogen activator (tPA) activity is reported [12].

In both physically active people and patients with peripheral arterial diseases exercise training enhances endogenous fibrinolytic activity, manifested as a decrease in plasminogen activator inhibitor (PAI-1) and an increase in tissue plasminogen activator (tPA) activity, suggesting that regular exercise may improve fibrinolytic activity [13,14]. During short-term exercise training PAI-1 levels were unchanged [13], and for enhancement of fibrinolysis daily physical activity of at least 35 minutes was required [15]. Opposing the concept of rest in DVT several studies have

shown benefits in reduction of pain and swelling, and improved quality of life by ambulation and walking in combination with anticoagulation and leg compression [6, 8, 16] in patients with DVT.

The aim of this randomized study was to answer the question weather supervised exercise improved recanalization of the thrombosis and/or the patient's symptoms.

PATIENTS and METHODS

PATIENTS

The present study was undertaken during September 2001 - March 2004. During this period DVT was diagnosed in 381 outpatients at Malmö University Hospital with a primary catchment area of 280 000 inhabitants. Our exclusion/inclusion criteria for having patients included that could be properly evaluated regarding thrombus score and likely to participate in a training programme meant that 309 subjects were non-eligible for randomization due to: known malignancy (n=33), language problems (n=10), age>75 years (n=98), previous DVT (n=54), DVT diagnosed only by ultrasonography (n=35), unwillingness to participate (n=18), or non-adequate phlebographies for scoring the severity of thrombosis (n=61).

The remaining eligible 72 patients were consecutively included and randomized to an exercise group or a conventional therapy group. Both groups treated with routine anticoagulation and class II compression stocking. The mean age was 54±14 years and 39 patients (52%) were men (Table 1).

All subjects provided written informed consent and agreed to accept random assignment to either exercise or control group and the study was approved by Lund University Ethical Committee.

Five patients were excluded from the final analysis: 4 patients from exercise group and 1 patient from control group because of declined participation during study period and refusal of repeat

phlebography. Neither of them showed any clinical complications.

STUDY DESIGN

The subjects were randomly assigned to one of two groups: An exercise group that received routine treatment with anticoagulation, class II compression stockings and additional daily walking exercise and weekly supervised exercise. The control group received routine anticoagulation and class II compression stockings but did not have exercise.

Routine anticoagulation included low molecular weight heparin (LMWH) subcutaneously given daily for 5-7 days (dalteparin, Fragmin®, 200IE/kg once daily, Pfizer AB, Täby, Sweden) and oral anticoagulation with warfarin (Waran®, Nycomed AB, Stockholm, Sweden) to therapeutic INR-levels (2-3) for 6-12 months.

All patients were examined by phlebography initially at diagnostic evaluation and the second time when the study protocol was finished after a six-month period. Deep vein thrombosis were classified as occurring at three different levels: proximal DVT, popliteal DVT and calf (distal) DVT (Table 2).

Proximal DVT was defined as DVT involving superior femoral or more proximal venous segments, with or without associated popliteal or calf DVT. Popliteal DVT was defined as DVT involving popliteal venous segments, with or without associated calf DVT. Calf (distal) DVT was defined as DVT involving anterior tibial or more distal venous segments.

Body mass index (BMI) was calculated as weight in kilograms (kg)m^2. Visual analog scale (VAS) was used initially and at follow-up as an overall quality of life assessment [17]. Thigh circumference was measured 15 cm above the knee joint, and calf circumference 15 cm below the knee joint. Balance test was performed, and quadriceps strength was measured at three different occasions: at inclusion, and at follow-up at one- and six-months.

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DVT-scoring of the phlebography was made according to Björgell [18, 19] at diagnostic evaluation and at the six-month follow-up phlebography.

SUPERVISED EXERCISE

All patients were immediately ambulated and treated as outpatients and additionally patients in the exercise group (n=32) agreed to at least 15-minute exercise training session at home every day during the six month study period. The daily exercise session intensity was 75W, and it was started approximately 5-7 days after DVT diagnosis. The exercise program was focused on the lower limbs, but some of exercises also involved the arms.

Upon study entry each patient in the exercise group was supervised in an in-hospital exercise program for 45 minutes. During the first month every subject in the exercise group had to attend one supervised exercise session per week led by an experienced physiotherapist at the Department of Vascular Diseases at Malmö University Hospital. After the first month and during the remaining study time all patients in the exercise group underwent one supervised exercise session per month. Supervised exercise session intensity was 125W, and the duration 45 minutes. This exercise program contained different training sections that involved both the lower and upper limbs and torso but focusing on exercises for the lower limbs. During each session there was a warm-up and cool-down periods consisting of 5 minutes supervised walking.

PHLEBOGRAPHIC SCORING SYSTEM

For the evaluation and distribution of the deep leg vein thrombosis the scoring system of Björgell and co-workers were used [18, 19]. This new scoring system divides the deep veins into 14 separate segments. Depending on the extension/severity of the DVT within each vein segment the severity was scored from 0 to 3 (0=no DVT, 1=less then one third, 2=one third or more but less

than two third, 3=two thirds or more of the length of the vein segment). A maximum score of 42 (=14x3) can thus be reached when there is a complete occlusion of the venous segments of the leg and pelvis. The phlebographic scoring was always determined by two investigators blinded regarding treatment. When there was a discrepancy between the investigators regarding the scoring, the examination was re-evaluated until agreement was reached.

STATISTICS

Results are expressed as median and range. Mann-Whitney's U-test was used to describe significance between groups of continuous variables and Chi-square test between nominal variables. The Wilcoxon test was used for comparisons within groups. P values <0.05 were considered to indicate statistical significance. For the statistical calculations Stat View 5.0 was used. Quality of life (QoL) assessment was made using an visual analogue scale from 0-100 mm estimating the overall QoL.

Prior to start of the study calculations on the size of the groups were made with the assumption of at least a 25 % difference in recanalization of occluded venous segments based on earlier studies. For an 80 % power this required 40 patients within each group and the study was aiming at inclusion of 100 individuals. However, the inclusion rate was lower than anticipated and blinded analysis showed lower phlebographic scores than assumed both initially and at 6 month follow-up. Inclusion was stopped.

RESULTS

There was no difference regarding age, body weigh, and BMI between the studied groups (Table 1). Nor were there any differences between groups regarding calf circumference of the affected

leg and overall quality of life estimated by the VAS-scale at inclusion. Neither was any difference found after the six-month follow-up period between the groups (Table 2).The phlebographic DVT-score was 9.8±8.3 vs. 10.2±8.3 at inclusion and 3.0±4.9 vs. 1.1±2.8 after six months in the exercise and the control group (p=NS). At the follow-up at one month there was a reduction in calf circumference of the affected leg compared to the initial measurements at inclusion (p=0.001; in the exercise group p=0.13 vs. control group p=0.002). This change was even more pronounced at six-month follow-up period (p=0.0002; exercise-group p=0.004 vs. control-group p=0.02).

No signs of recurrent DVT, pulmonary embolism or other complications were noted for any participant during the six-month follow-up period.

No significant differences were found between groups regarding measurements of muscle strength and others variables at the inclusion time and likewise, after six-month follow-up period. When the changes in thigh and calf circumference (Δ-values) in the 2 groups were compared, no significant differences were found.

Overall quality of life was improved during the follow-up but without any difference between groups (Table 2).

DISCUSSION

Despite the fact that deep venous thrombosis (DVT) is a common disease there are few studies that have addressed the benefits or risks of exercise and early ambulation in DVT patients. Early exercise has been proposed to be beneficial and to increase recanalization of thrombosis, but also to be harmful by dislodging clots and increasing the risk for PE. Different attitudes towards early mobilisation in DVT are therefore seen. The introduction of out of hospital treatment with LMWH for selected patients without other severe diseases has proven that early ambulation to be

safe. Several studies have reported such treatment as safe, feasible, practicable and cost-effective and with the same outcome as in-hospital treatment [20-25]. Only few studies of more active exercise as a part of the treatment of DVT have been published. Partsch et al [6] showed in a randomised controlled trial a significant benefit of walking exercise combined with compression stockings compared to bed-rest in patients with proximal DVT. The exercise group had a more rapid resolution of pain and swelling compared to patients with bed-rest. However, follow-up was only nine-days and was limited by a fairly low number of patients. In our study first follow-up was later and we were not able to verify their findings of an early improvement. There have also been reports on improvement of well-being and DVT-related quality of life also at a nine day follow-up and this improvement was more pronounced in patients with proximal DVT treated with early ambulation, walking exercises, compressions stockings/ bandages in addition to LMWH and oral anticoagulation [8].

In our study the main outcome measure was recanalization of occluded vein segments. For this analysis we used a thrombosis severity score. A number of phlebographic scoring systems can be applied to assess the thrombotic burden of DVT. Apart from the methods of Marder [26] and Arnesen [27] there is also a third scoring system from a subcommittee of venous disease 1988 [28]. These are not optimal in evaluation of the severity of the thrombosis however, the new scoring system of Björgell and co-workers [18, 19] used in this study allows a more detailed description, includes evaluation of the severity and also takes into account the distribution of deep leg vein thrombosis.

In spite of this we were unable to detect any difference between groups regarding recanalization of occluded venous segments. Maybe our study groups included too few patients and the proportion of patients with popliteal and calf vein thrombosis in which recanalization was more complete dominated. The number of patients with proximal DVT might have been to few to

allow us to document any benefit of exercise.

Despite that we were unable to verify benefits of early exercises as reported by Partsch et al [6] and Blattler & Partsch [8], the results from our study confirms that early exercise and/or ambulation in combination with anticoagulation and compression stockings do not increase the risk of complications and is safe for the majority of patients with DVT. It also seems theoretically advantageous to improve one of the corner stones in Virchow´s triad - venous flow by exercises to prevent further thrombus propagation.

This concept and safety of early ambulation/exercise is also supported by other studies of walking exercises [29, 30], and by randomized studies showing no increased frequency of sub clinically scintigraphically detected PE in patients that had early mobilisation compared to bed-rest [4, 7]. Our study is limited due to the low number of patients included, but while no substantial benefit was seen from exercise regarding recanalization, no obvious complications could be attributed to early exercise either.

The strength of our study is that it was prospective with random assignment to groups of exercise or not, in addition to optimal anticoagulation therapy and compression stockings. Furthermore all subjects in the exercise group underwent supervised exercise sessions by our experienced physiotherapist to ensure that physical activity was focused on the lower extremity, but also included all major muscle groups. The limited number of patients included and their relative low thrombotic severity score reduces our possibilities to optimally analyse the effect of exercise. This is partly due to the strict inclusion criteria set-up for this study. The number proximal thrombosis showing less optimal “spontaneous” recanalization should have been larger but the

material includes every consecutive out-patient that was eligible and treated at our hospital.

In summary early mobilisation and even active exercises can be safely started almost immediately after a DVT. However, recanalization of occluded vein segments or swelling of the affected leg was not improved by daily physical exercises.

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Table 1. Patient characteristics and distribution of deep vein thrombi for patients in the exercise group and the control group. Median (range); BMI= Body mass index.

Variable	**Exercise group (n=36)**	**Control group (n=36)**
Age (years)	54(25-75)	57(25-74)
Weight (kg)	82(50-120)	78(51-104)
BMI (kg/m2)	27±4.4	25(20-32.7)
Proximal thrombosis (n=28)	14(38%)	15(41.6%)
Popliteal thrombosis (n=20)	13(36%)	7(19%)
Distal thrombosis (n=20)	9(25%)	14(38.8%)

Table 2. Results in patients with deep vein thrombosis randomised to exercise in and control groups. Results presented as Median (range), VAS= Visual analog scale.

Variable	**Excercise group (n=32)**	**Control group (n=35)**	**P-value**
Calf circumference affected leg - at inclusion (cm)	38(33.5-49)	37.5(32-45)	NS
Calf circumference affected leg -1 month (cm)	38(32-51.5)	36.5(32-44)	NS
Calf circumference affected leg -6 months (cm)	38(25.5-48)	36(32.5-44)	NS
VAS -at inclusion (0-100mm)	42(1-88)	45.5(9-93)	NS
VAS -1 month (0-100mm)	13.5(0-83)	12(0-71)	NS
VAS - 6 months (0-100mm)	4(0-74)	7.5(0-95)	NS
Phlebographic score – at inclusion (0-42)	6(1-30)	6.5(1-26)	NS
Phlebographic score – at 6 months (0-42)	0(0-19)	0(0-13)	NS