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ANTICOAGULANT THERAPY IN DEEP VENOUS THROMBOSIS. A RANDOMIZED CONTROLLED STUDY

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Abstract Ninety patients with venographically proven deep venous thrombosis(DVT) but without clinical signs of pulmonary embolism(PE) were randomized into two different treatment regimes to compare the safety and efficacy of continuous intravenous heparin and oral anticoagulant(AC) treatment versus non-AC treatment. All patients in the two treatment groups were actively mobilized from the day of admission and wore graduated compressing stockings.In the non-AC-group the patients were treated with phenylbutazone for ten days.Treatment with heparin was maintained for 6 days and oral AC treatment was given from the third day and continued for 3 months. Venography was repeated after 30 days. A perfusion-ventilation lung scan was performed on day 1-2, 10 and 60.In fifty-nine patients a revenography was performed, twentynine in the AC-group and thirty in the non-AC group.For distal veins regression was found in nine and eight respectively (4,4% in favour of AC,95% confidence limit 27,5% to - 18,7%) and in proximal veins regression was found in five and eight, respectively (10,9% in favour of AC, 95% confidence limit 32,0% to -10,1%).No difference in lung scans was found after 10 days (0.8% in favour of AC, 95% confidence limit 21,5% to -19,9%) or after 60 days (3,3% in favour of non-AC treatment, 95% confidence limit 21,8% to -28,5%). In the AC group the incidence of bleeding complications was 8,3%. No side-effects of phenylbutazone was found.
The present controlled clinical study demonstrated no effect of AC-treatment on DVT progression in actively mobilized patients wearing graduated compressing stockings when compared to a non-AC treated group receiving analgetic therapy with phenylbutazone. However, the patient population of the study is relatively small with wide confidence intervals for differences between groups. Before more general recommendations can be made, a large scale placebo-controlled study is needed to evaluate the possible effect of AC-treatment in DVT patients, who can be mobilized from the first day.

Keywords: Deep venous thrombosis, anticoagulation, mobilization.
Abbreviations: AC,anticoagulation; DVT,deep venous thrombosis; PE,pulmonary embolism.
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Prophylactic treatment with anticoagulant drugs reduces the frequency of deep venous thrombosis (DVT) as well as pulmonary embolism (PE) in risk patients, i.e. during major surgery, in stroke and heart disease etc. (1). Heparin and oral anticoagulants are also recommended for the treatment of venous thromboembolism, and this indication was primarily based on a small trial with clinical diagnosis of DVT and PE (2).

Several studies comparing different anticoagulant(AC) treatment regimes have shown that subcutaneous heparin is more effective in helping lysis of existing thrombus in DVT than intravenous heparin (3), extension of thrombosis in proximal DVT was significantly reduced by heparin treatment as compared to oral AC treatment (4) and low-dose subcutaneous heparin was less effective than adjusted-dose warfarin in preventing recurrent venous thromboembolism in DVT (5). Treatment of DVT confined to the distal veins with short-term heparin was less effective than heparin followed by oral AC treatment (6). The need of valid controlled clinical trials has been stressed (7).

The aim of the present randomized clinical study has been to evaluate the efficacy of AC treatment versus no AC treatment in DVT patients actively mobilized from the first day of hospitalization.

MATERIALS AND METHODS.

The study population consists of consecutive patients with clinical signs of DVT. The duration of symptoms was less than 6 days. The patients were randomly allocated to either AC- or non-AC treatment. The study was designed to have an open therapeutic procedure and a blinded control. All participants gave written informed consent for the study, which was approved by the Ethical Review Board of the County of Aarhus. Patients were excluded if they had clinical symptoms of PE such as dyspnoea, tachycardia, chest pain, hemoptysis, ECG changes, hypoxia and hypocapnia or if they were unable to be actively mobilized. A chest X-ray was performed at admission, and no infiltration was registered on included patients.

Within 24 hrs after admittance an ascending venography was performed using the method of Rabinov and Paulin (8). Contrast medium (Isopaque^{R} Amin 280) 50-150 ml was injected into a dorsal foot vein, while the superficial veins were compressed. The distal and femoral veins as well as the distal part of the iliac veins were visualized. The venography was repeated within 30 days. The venograms were evaluated separately by two experienced radiologists, who were blinded to the treatment of the patients. In the evaluation of the venograms a distinct outlined defect in contrast-filled veins or a non-filled deep venous trunk were considered to represent a thrombus. In the comparison between the pre- and post treatment venograms special notice was taken of a proximal propagation of the thrombus, and it was assessed, whether new defects had occurred or the thrombus had increased in size, decreased or was unchanged.

Baseline perfusion and ventilation scans of the lungs were performed within 48 hours of randomization and repeated after 10 and 60 days. For ventilation lung scan a rebreathing technique was used with a spirometer (Godart expirograph, type EP 62,001) containing 10 l atmospheric air with 740 mBq (20 mCi) ^{133}Xe (Studsvik AB atomic energy, Sweden). Four views (anterior-posterior, posterior-anterior, right and left lateral 45° oblique) were obtained. Imaging was performed with a gamma camera (Pho-gamma 111, high performance

with 16,000 holes diverging collimator, Searle Radiographics).

Immediately after termination of the ventilation scan, a perfusion scan was performed. Thirtyseven mBq (1 mCi) of ^{99m}Tc-labelled microaggregated albumin (Hoechst) were injected intravenously. Perfusion images were then obtained in the same projections as the ventilation scans. The scintigrams were interpreted in random order by two experienced physiologists, who were blinded to the method of treatment. Abnormal findings were classified according to the size of the defect (one, two or more lobi) and compared with the ventilation scan. If ventilation occurred at the perfusion defect it was classified as ventilation-perfusion mismatch indicating a PE. The three lung scans were compared, and it was decided, whether a new defect had occurred or the embolus had propagated, regressed or was unchanged.

Regimens.
Sodium heparin (Leo Pharmaceutical Products, Copenhagen, Denmark) was administered intravenously. The treatment was initiated by a bolus injection of 10,000 i.u., followed by continuous infusion. For each twelve hrs 20,000 units of heparin were dissolved in 500 ml of 5% dextrose, and the rate of infusion was controlled by means of a drop control device with a mobile infusion pump and adjusted to keep the activated partial thromboplastin time (APTT) at 1.5 to 2.5 times the control value. The APTT was measured with Activated Thrombofax reagent (Ortho Diagnostics) (reference value < 40 sec). The APTT was determined before start of heparin therapy, 6 hours after start of therapy and dose adjustment and routinely once daily. Phenprocoumon (Marcoumar^{R}, Roche) was given from the third day. Heparin treatment was continued for at least 6 days, or until the prothrombin time ad modum Owren (9)(Thrombotest^{TM}) had reached the therapeutic level 10 to 30% of normal (International normalized ratio (INR) between 2.0 - 4.3). The oral anticoagulant treatment was continued for 3 months.

In the non-AC group the patients were treated with phenylbutazone (Arthrizin^{R}, Leo Pharmaceutical Products, Copenhagen, Denmark) 200 mg 3 times at the day of ad-mission, and then 100 mg 3 times daily for the following 9 days.
All patients in the two treatment groups were actively mobilized from the day of admission and wore graduated compressing stockings (TED-stockings, Kendall Company, Boston, USA).

Outcome events.
The primary endpoints were propagation or development of new venous thrombo-embolic events as indicated by either venography after 30 days or lung scans after 10 and 60 days. The patients were followed in the out-patient clinic 3 and 12 months after the initiation of treatment. The presence of DVT-recurrence or PE symptoms during the first 3 months and deaths within 12 months were recorded. Bleeding episodes were registered and called major, if they occurred within a body cavity (i.e. retroperitoneum), required blood transfusion and/or led to discontinuation of AC treatment. All other bleeding episodes were called minor.

Statistical analysis.
Frequency of propagated, regressed or unchanged thromboembolic events and bleeding episodes in the two treatment groups were compared using the Chi-squared test or Fisher's exact test. A p-level of <0.05 was considered significant.

RESULTS

One hundred and twelve consecutively, eligible patients entered the trial. Ascending venography was negative in 19 patients - nine patients in the AC-group and ten in the non-AC-group. In one patient venography could not be performed and two further patients were randomized by failure - one with clinical signs of PE and one without clinical signs of DVT. Thus 90 patients entered the study, 48 assigned to the AC-group and 42 to the non-AC-group.

Baseline characteristics of the patients randomization are shown in Tables I - II. There were no differences between the groups according to sex, age, thrombotic risk-factors, underlying disorders, distribution of distal and proximal (popliteal or more proximal) DVT as well as asymptomatic PE.

Therapeutic efficacy.

Venography.
Ten patients dropped out before revenography after 30 days (mean 32.4 days), 9 in the AC-group and 1 in the non-AC-group (Table III).

Of the remaining 80 patients 59 had a revenography - 29 in the AC-group and 30 in the non-AC-group. Twentyone patients - 10 in the AC-group and 11 in the non-AC-group -had no venographic control, due to side-effects of contrast medium, technical or administrative

TABLE I

Characteristics of the 90 Randomized Patients with a Diagnosis of Deep Venous Thrombosis (DVT).

	Anticoagulant treatment (n=48)	No anticoagulant treatment (n=42)	Total (n=90)
Sex (male/female)	30/18	28/14	
Age(years;median and range)	57(17-84)	57(20-82)	
Disease:			
Malignant	4	7	11
Orthopedic	14	9	23
Cardiovascular	3	2	5
Vein insufficiency	5	5	10
Non-malignant hematological	0	2	2
Alcoholic abuse	1	1	2
Other diseases	6	1	7
No essential disease	15	15	30

TABLE II

Localization of Deep Venous Thrombosis (DVT) and Frequency of Silent Pulmonary Embolism (PE).

	Anticoagulant treatment (n=48)	No anticoagulant treatment (n=42)	Total (n=90)
DVT localization:			
Distal	9	7	16
Proximal	39	35	74
Lung scintigraphy:			
Positive	23	19	42
Negative	23	22	45
No scintigraphy	2	1	3

reasons. No difference could be detected between patients who had and patients who had not had a venographical control according to age, sex or risk factors. No clinical signs of DVT recurrence were registered in the patients without revenography. The repeated venography showed no significant difference in progression and regression rates between the two groups (Table IV). The difference between the index of effectiveness was insignificant, but in favour of AC treatment and was for distal veins 4.4% (95% confidence interval 27.5% to -18.7%) and for proximal 10.9% (95% confidence interval 32.0% to -10.1%).

TABLE III

The Cause of Drop Out Within 30 Days.

Reason	Anticoagulant treatment	No anticoagulant treatment	Total
Bleeding	5	0	5
Risk during anticoagulation	1	0	1
Generel weakness	1	1	2
Patient´s own wish	1	0	1
Allergy to heparin or X-ray contrast	1	0	1
Total	9	1	10

TABLE IV

Venographic status in distal and proximal veins at venography after 30 days.

	Anticoagulant treatment (n=48)	No anticoagulant treatment (n=42)
Distal veins:		
Progression or new lesions	15	17
Unchanged	5	5
Regression	9	8
Proximal veins:		
Progression or new lesions	6	8
Unchanged	15	17
Regression	8	5
Drop outs	9	1
No venographic control	10	11

Lung scintigraphy.
Eightyseven of the 90 patients included in the study had a ventilation-perfusion lung scan performed at inclusion. For technical (one patient) and administrative (two patients) reasons three patients had no baseline lung scan performed - two in the AC-group and one in the non-AC group. A positive lung scan was found in 49% of patients with a frequency of 33% among patients with thrombosis confined to distal veins and 53% in patients with femoral extension of the thrombus. Control lung scan after 10 days was performed in 80 of the patients with 39 non-AC and 41 AC patients, and 60 patients had the lung scan repeated after 60 days with 30 non-AC and 30 AC patients. Control lung scan did not show any difference between the two treatment groups in the fate of PE (table V). At the first control after 10 days the difference was 0.8% (95% confidence interval 21.5% to -19.9%) in favour of AC treatment, and at 60 days 3.3% (95% confidence interval 21.8% to -28.5%) in favour of non-AC treatment.

Clinical evaluation.
During the 3 months of AC treatment two patients developed clinical signs of PE. Autopsy was performed in one patient, who died from PE with heart disease as a contributing cause and PE was confirmed by lung scan in the other patient. Three patients had clinical signs of DVT recurrence, and one of these patients with carcinoma of the lung died within 2½ month from the malignant disease. The DVT was not verified by phlebography.

During the first 3 months nine patients in the non-AC-group - all with proximal DVT - developed clinical signs of DVT-recurrence. Of these one patient had PE symptoms as well with the diagnosis verified by lung scan. This patient was anticoagulated. Five of

TABLE V

Lung Scintigraphic Status After 10 and 60 Days.

	Anticoagulant treatment (n=48)	No anticoagulant treatment (n=42)
Lung scintigraphy, 10 days:		
Progression or new lesions	6	3
Unchanged	21	23
Regression	14	13
Drop outs	7	1
No scintgraphic control	0	2
Lung scintigraphy, 60 days:		
Progression or new lesions	1	1
Unchanged	16	15
Regression	13	14
Drop-outs	9	2
No scintigraphic control	8	10
Patient died	1	0

the patients with clinical signs of DVT showed progression of thrombosis on the phlebografic control at 30 days, while 4 patients had no phlebographic control. One of these patients developed phlegmasia coerulea dolens. She was treated for one year with anticoagulant drugs, and developed no clinical signs of venous insufficiency. The remaining 7 patients had TED-stockings and were actively mobilized, while receiving phenylbutazone for 10 days, and their symptoms regressed.

All these patients had proximal DVT. Totally, as registered by venography, lung scintigraphy or clinically, 22 patients in the AC-group and 23 patient in the non-AC-group developed signs of thrombosis progression or new lesion formation during the 3 month-periode (Table VI). Within 12 months six patients died in the AC-group - one from PE, and seven patients died in the non-AC-group - none from PE.

Anticoagulant efficacy.

Only 43 of 264 APTT measurements were below the therapeutic level. No relation between APTT-level and treatment efficacy as indicated by venography and lungscans or bleeding complications was found. During phenprocoumon treatment 70% of prothrombin time measurements were within the therapeutic range.

Complications.

On treatment with anticoagulants major bleeding complications occurred in four patients (8.3%), and minor bleeding complications in two patients (4.2%).

TABLE VI

Progression or New Lesion Formation in Patients With Deep Venous Thrombosis (DVT) and/or Pulmonary Embolism (PE) Registered by Phlebography, Lung Scan or Clinically.

Venous thromboembolism	Anticoagulant treatment (n=48)	No anticoagulant treatment (n=42)
No clinical signs:		
DVT	14	12
PE	3	1
DVT and PE	1	1
Clinical signs:		
DVT	1	3
PE	1	0
DVT and PE	1	2*
DVT, no phlebography confirmation	1	4
Total number of events	22	23

* One patient had clinical signs of DVT verified by phlebography and clinically silent PE.

Five patients treated with phenylbutazone developed signs of cardiac insufficiency demanding diuretic therapy. In none of the cases phenylbutazone was withdrawn. An universal exanthema developed in two patients during phenylbutazone therapy and in one patient during heparin treatment. After the venography 2 patients had an itching rash possible due to the radiographic contrast medium.

DISCUSSION

The main therapeutic goals in the treatment of DVT are to prevent extension of venous thrombosis, to prevent PE, and to facilitate restoration of patent veins reducing the risk of developing chronic venous insufficiency.

Deep venous thrombosis.

Despite the use of AC treatment for more than 40 years a wide difference in recommendations for drug administration exists (7,10). Since the study by Barritt and Jordan (2), who used an untreated control group in an open study on efficacy of AC therapy in patients with clinical PE, clinical studies with a non-AC-group have not been performed. They found significant more cases of clinical recurrent PE as well as fatal PE in the untreated group. However, a clinical PE diagnosis is very unreliable with a predictive value as tested by angiography of about 25% (11,12).

We could demonstrate no significant difference in the fate of venous thrombosis between an AC- and a non-AC-group controlled with venography and lung scintigraphy. During the three months control period, there was slightly more cases of clinical DVT-recurrence in the non-AC group as compared to the AC group, but all but one regressed during a repeated treatment with phenylbutazone and TED-stockings.

In the present study we used phenylbutazone to reduce oedema and pain during mobilization in the non-AC group of patients. Higher dosage of phenylbutazone than used here may have some antithrombotic potential (13).

All our patients were mobilized from the first day using graduated compressing stockings. Venous thrombosis may propagate during continued bed rest, and a beneficial effect of active mobilization in the primary as well as the secondary prophylaxis against DVT has been suggested (14), but not confirmed in controlled trials. In addition, graduated compressing stockings have proved to be effective in the protection against chronical venous insufficiency in patients with DVT (15).

In an open swedish study with initial heparin therapy for 6-7 days a comparison was made between AC and non-AC treatment of patients with venographically verified DVT in the distal veins (6). No difference in regression rate of thrombosis evaluated by repeated ^{99m}Tc-plasmin scan of the legs was found, but more cases of clinical recurrences were registered in the non-AC-group. It has been argued, that cessation of heparin therapy in the non-AC group may have increased the risk of thromboembolism (16). Subcutaneously administrated heparin has been compared with intravenously administrated heparin, but the results have been contradictory (17). In a recent metaanalysis of eight clinical trials, it was concluded, that subcutaneous heparin is more effective and at least as safe as continuous intravenous infusion of heparin (17). Hull et al. (18) found a higher rate of recurrent DVT in the subcutaneous as compared to the intravenous heparin group and related it to a lower intensity of the subcutaneous heparin regimen. The groups were not homogenous with "silent" DVT in 39% of patients and 6 of the 11 recurrent DVT events observed in the subcutaneous group actually occurred at least one week after heparin treatment had been completed making it questionable to attribute these events to an inadequate initial heparin treatment.

Adjusted subcutaneous heparin was significantly more effective than oral AC treatment in the initial treatment of proximal-vein thrombosis (4), while low-dose subcutaneous heparin is less effective (5). The optimal duration of heparin treatment considering safety and cost was shown to be on average 5 days (19), and 10 days of intravenous heparin was not more effective than 5 days of therapy with oral AC treatment initiated simultaneously (20). However, Krupski et al. (21) and Solis et al. (22) failed to demonstrate any effect of heparin treatment on thrombosis progression in patients with symptomatic DVT and asymptomatic distal DVT, respectively.

Low-molecular-weight heparin administrated subcutaneously was shown ot be at least as effective and more safe than intravenous unfractionated heparin in treatment of DVT (23,24)

Pulmonary embolism.
Perfusion-ventilation lung scan performed before initiation of study medication showed asymptomatic PE in 49% of the patients with symptomatic DVT diagnosed by venography (present study). Control perfusion-ventilation lung scan performed at the 10th and the 60th day on treatment demonstrated no difference between the two groups in the fate of pulmonary emboli. One patient in the AC group died from PE, and clinical signs of PE developed in another 2 patients with one in each group.
Huisman et al. (25) treating DVT with heparin found no effect in 32 % and deterioration in 8% of patients with asymptomatic PE using perfusion lung scintigraphies. Repeated perfusion lung scans during the first 15 days in patients with PE verified by pulmonary angiography showed a recurrence rate of 4% during AC-treatment. This low recurrence rate might be explained by a low frequency of severe underlying diseases in the patient population studied. None of the patients suffered from congestive heart disease and only 4% from malignant diseases, which are considered as the most important predictors for a poor prognosis in PE (27). In the present study a low frequency of recurrent PE was registered with no difference between the AC- and non-AC-group, and after 1 year no difference in mortality between the two groups could be registered.

Complications.
The risk of major bleeding complications in patients receiving intravenous heparin infusion ranges from 1 - 33% (4), and during long-term AC treatment the risk is on average 8,1% (28). An incidence of 8.3% was found during AC treatment in the present study and no relation to APTT-values was found.
In the non-AC-group receiving phenylbutazone the frequency of side-effects was small and only one patient dropped out. Phenylbutazone-induced agranulocytosis was not seen.

Conclusions.
The present controlled clinical study compared AC treatment with no AC treatment in patients with DVT verified by venography. All patients were actively mobilized from the first day of hospitalization, and wore graduated compressing stockings. No difference between the two treatment regimens on thrombosis progression could be demonstrated.
The patient population was relatively small with wide confidence intervals for the differences between groups, and therefore a large scale placebo-controlled study is mandatory to evaluate the efficacy of AC therapy in DVT patients, who can be mobilized from the first day.

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