INTRODUCTION

Deep vein thrombosis (DVT) is a frequent medical condition (annual incidence 0.2% of the urban population)¹ and the sequelae of DVT can be harmful and have a great impact on patients’ quality of life. Chronic venous insufficiency, when acquired after an episode of DVT is known as post thrombotic syndrome (PTS). Complaints in PTS range from a mild discomfort to pain, restless legs, pigmentation disorders and finally ulcer cruris venosum, which is considered the terminal symptom of PTS.¹ Despite anticoagulant treatment of

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SUMMARY:
Compression therapy using medical elastic compression stockings (MECS) determine an absolute reduction rate of PTS with 25%. There are 2 main types of PTS: the reflux type (70%) and the obstruction type (~10%). Partial recanalisation occurs in the majority of DVT cases. The main hemodynamic determinant factor of PTS is represented by the increased venous pressure in the affected inferior limb.
We made a study protocol on the influence of the duration of compression therapy in the development of post-thrombotic syndrome, evaluated by objective measurable parameters.

Key Words: PTS, venous hypertension, venous valves, MECS.

STUDII PROSPECTIVE – ACTUALITATI IN DIAGNOSTICUL SI MANAGEMENTUL TROMBOZEI VENOASE PROFUNDE SI AL SINDROMULUI POSTTROMBOTIC
Partea a 3-a: Studiu prospectiv al sindromului posttrombotic la pacienþii nou diagnosticaþi cu DVT: rolul important al MECS pentru prevenirea ºi tratamentul PTS

Rezumat:
Există 2 tipuri principale de sindrom posttrombotic: cu reflux (70%) si cu obstructie (~10%). Recanalizarea partiala a sistemului venos profund apare in majoritatea cazurilor cu DVT. Principalul factor determinand al PTS este presiunea venoasa crescuta la nivelul membrului inferior afectat. Terapia compresiva folosind ciorapii elasti ci medicali (MECS) determina reducerea incidenþei sindromului posttrombotic (PTS) cu 25% la pacienþii trataþi correspunzator si urmarit pe o perioada de 2 ani. Am realizat un protocol de studiu asupra influenþei duratei compresiei în dezvoltarea sindromului posttrombotic evaluat prin parametri măsurabili.

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DVT, the frequency of ulcer cruris is as high as in the 1970s of the previous century indicating the persistence of a serious social economic problem. The statement of Charpy and Audier (1956) is still very true today: “the agony of the post-thrombotic patient begins as soon as he/she is –seemingly cured- released from hospital”. The studies of Brandjes et al. and Prandoni et al. have clearly demonstrated that about half of the DVT patient do not develop PTS in the control group, and that compression therapy using medical elastic compression stockings (MECS) decreases this incidence with 50% (from circa 50 to 25% indicating an absolute reduction rate of 25%) during an observation and treatment period of 2 years following DVT. It is unknown what should be done with these patients after 2 years. Unfortunately, this evidence-based knowledge is not applied generally in daily practice. Family doctors and internists usually treat the acute phase of DVT with anticoagulants for at least 3 to 6 months. Physicians with interest and expertise in phlebology are usually confronted much later and frequently too late with overt post-thrombotic complications of DVT.

There is evidence from two prospective studies that compression therapy with MECS is highly effective in reducing the frequency of PTS in DVT patient. In view of this, there are three interesting and yet unanswered questions in the treatment of DVT:

1. Which DVT patient has a clear indication for long-term compression therapy to prevent PTS after the initial treatment in the acute phase of DVT?
2. Is 6 months the appropriate point in time to determine candidates to develop PTS?
3. Is continuing compression therapy after 2 years effective in the prevention of PTS?

RECANALIZATION OF THROMBOSED VEINS IN DVT PATIENTS

The treatment of a patient with DVT is primarily targeted to prevent the acute complications, such as pulmonary embolism, which may even be fatal. In addition, anticoagulant treatment is given to stop thrombus growth. Data from literature indicate that rapid thrombus resolution and full re-canalisation of the vein reduces the chance of vein walls and valves damage. This concept indicates the need for a rapid and adequate anticoagulant treatment as soon as the diagnosis of DVT is made. Recent studies show that early mobilisation of the patient, adequate anticoagulant therapy and immediate compression treatment with MECS reduces significantly the chance for PTS. There are no data available indicating the time needed to reach final (i.e. maximal or full) re-canalisation. Some authors propose this process takes approximately one year, but most experts agree that after 2 years no further re-canalisation can be expected. It is commonly accepted that the re-canalisation process is completed between 3 months to 2 years, depending on the severity of DVT and the presence or absence of transient or persistent risk factors for thrombosis recurrence and PTS.

THE POST-THROMBOTIC SYNDROME (PTS)

The incidence of PTS in DVT patients after discontinuation of anticoagulant treatment is approximately 50% after 2 years follow-up. Phlebologists generally distinguish two main types of PTS:

1. The reflux type (circa 90%)
2. The obstruction type (circa 10%)

In a substantial number of patients only partial re-canalisation occurs (as opposed to either complete obstruction or complete re-canalisation). Duplex ultrasound imaging can assess this.

DVT patients with re-canalisation can be divided in two groups:

1. Those with functional (intact) vein valves
2. Those with dysfunctional vein valves

Dysfunctional vein valves result in reflux and ultimately in increased venous pressure, which is the main hemodynamic determinant of PTS. Patients with re-canalisation after DVT, but without reflux or venous hypertension, might be candidates for discontinuation of compression therapy within the period of 2 years.

The reflux problem

The blood from the vein of the legs is pumped back to the heart by different mechanisms of which the “calf muscle pump” during walking is the most important one. The heart is only a pressure pump and not a sucking pump. When reflux is due to the loss of functional vein valves in re-canalised veins as happens in PTS, the muscle pump during walking will be less effective. As long as the capacity of the calf muscle can compensate for the reflux, there will be no visible signs of PTS in the involved leg of the DVT patient. In a number of patients the reflux will decompensate the venous system of the leg after a shorter or longer period following DVT. Decompensation signifies the situation in which the calf muscle pump during walking is insufficient to pump back venous blood to the heart, which will result in an increased venous pressure during walking (increased ambulant pressure).
The pressure problem and reflux or obstruction

In physiological conditions, the venous pressure in the legs while standing (standing venous pressure) is the same for healthy and PTS individuals. The venous valves are opened in standing position. Therefore, the standing venous pressure corresponds with the hydrostatic pressure of the right atrium to the place of measurement in the veins of the lower leg (approximately 80 mm Hg). The ambulant venous pressure in PTS patient, on the contrary, differs from the healthy individual. In healthy individuals, the ambulant venous pressure will decrease to about 15 to 20 mm Hg, but will decrease significantly less in PTS patients. This phenomenon is defined as venous hypertension.

Venous hypertension in PTS patients is responsible for the changes of the microcirculation in the skin of the lower leg. These changes of the microcirculation lead to leakage of water, proteins and erythrocytes which clinically present as edema, pigmentation, atrophy blanche, dermato- and liposclerosis, chronic compartment syndrome and ulcer cruris venosum.

The obstruction problem

Patients with obstructive PTS often have severe signs of venous insufficiency, for which compression therapy is recommended. The aim of treatment is the prevention of PTS complications such as dermato and liposclerosis, atrophy blanche, stiffness of the ankle joint and ulcer cruris venosum. When occlusion of distal veins is present, compression therapy will not always be feasible, because it may compromise the collateral veins too much and impair muscle pump function, resulting in impaired flow of venous blood from the lower leg to the heart. In addition to the pressure problem patients with PTS also suffer from increased venous resistance, which leads to increased ambulatory venous pressure and a longer transmission time of the venous blood. For patients with obstruction of the iliac vein, desobstruction and stenting of the vein may be considered. The long-term results are yet unknown, but most experts recommend additional long-term or even life-long anticoagulant treatment in case this treatment is given.

TYPE AND DURATION OF THE STUDY

We propose a prospective randomized clinical outcome study with a follow-up period of 4 to 5 years. All patients with DVT at time of diagnosis aged between 18-80 years are included, all DVT patients will immediately receive anticoagulant and compression therapy. In case of pronounced edema, compression therapy will consist of short stretch bandages until the edema is relieved. In case of minor or no edema, compression therapy with MECS will be prescribed and MECS should be "flat knitted" stockings pressure class III with a high resistance coefficient. Objective documentation will consist of phlebological controls, duplex ultrasound imaging and ambulant venous pressure measurements (when indicated) and will take place at 0,

The Post-Thrombotic Syndrome: PTS

PTS study design: type and duration of treatment

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Figure 1 PTS study design.
6 and 12 months and subsequently every year. Based on these objective measurements and assessments, DVT patients will be risk stratified at 6 months post-DVT for continuation or discontinuation of compression therapy with MECS according to the study design (figure 1).

Criteria of exclusion: patients with short life expectancy (<4 yr), recurrent ipsilateral DVT, leg ulcers, ankle-brachial index <0.7 or paralysis of the leg. Patients who are not ambulant, have a contraindication for the use of MECS (e.g. advanced-stage peripheral arterial insufficiency) or are not willing to wear them, are also excluded.

Objective measurement of clinical symptoms, the degree of re-canalisation and reflux (when indicated) will take place at 6 and 12 months after diagnosis of DVT and subsequently after 2, 3 and 4 years.

Clinical signs and symptoms of chronic venous insufficiency and PTS will be recorded according to a standardized scoring systems including the CEAP, Widmer or Vialta score.

Obstruction, re-canalisation and the presence or absence of reflux will be assessed by duplex ultrasound imaging of the deep veins of the leg.

In all patients with reflux on duplex ultrasound, additional measurement of ambulant venous pressure will be performed, by means of direct intravenous pressure measurement.

All DVT patients will be assessed for severity according to the modified criteria of Wells at the time of diagnosis.

All DVT patients will be treated immediately with low molecular weight heparin followed by vitamin K antagonist (VKA) for 6 months. This duration of VKA treatment is based on risk stratification according to current recommendations. All DVT patients will be treated immediately with compression therapy (MECS) for 6 months. Patients with re-canalisation and without reflux will not continue MECS treatment and will remain in follow-up for at least 4 years.

All patients with obstruction on duplex ultrasound imaging (no re-canalisation) will receive compression therapy (MECS) for 2 years. After 2 years a randomization will take place for continuation and discontinuation of MECS for at least another 2 years.

DVT patients with re-canalisation at 6 months post-DVT will be risk stratified and subdivided in those without reflux and those with reflux on duplex ultrasound imaging.

Patients with reflux but normal venous pressure (no venous hypertension) will be randomized for MECS vs. no treatment for 2 years.

Patients with reflux and increased venous pressure (venous hypertension) will receive compression therapy (MECS) for 2 years. After 2 years randomization will take place for continuation vs. discontinuation of MECS for another 2 years.

REFERENCES

References (continued):


