Aetiology and treatment of venous thromboembolism

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Home Treatment of Deep Venous Thrombosis: From Research to Daily Practice

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Abstract
The treatment of deep venous thrombosis is reviewed, with a specific focus on home treatment compared to hospitalisation. Home treatment of deep venous thrombosis is feasible, but there are some essential requirements to be fulfilled. Home care physicians may take part in this multidisciplinary task.
Introduction

Deep venous thrombosis (DVT) is a well known clinical disorder with an annual incidence of 1 to 2 per 1000 inhabitants in Western societies. The incidence of DVT rises with advancing age from 0.02 per 1000 individuals younger than 20 years of age to 8.1 per 1000 in the elderly (above the age of 80). Despite treatment, DVT is associated with significant morbidity (e.g. post-thrombotic syndrome and recurrent disease) as well as mortality due to pulmonary embolism.

In the past decades, important developments in the treatment of venous thromboembolism have made it possible to shift DVT treatment from an in-hospital to an outpatient setting.

Although DVT and pulmonary embolism are regarded to be a single clinicopathological entity, we will limit ourselves to a historical overview of the improvements in the treatment of DVT. The impact on patient satisfaction, as well as economic aspects of these improvements will be discussed. Finally, we will review essential requirements for outpatient treatment of this disorder.

Treatment of Deep venous thrombosis

In the sixties of the past century a landmark trial showed that death could be prevented in patients with pulmonary embolism who were treated with anticoagulant agents. Since then, it is generally accepted that venous thromboembolism has to be treated with these drugs in order to prevent thrombus extension, pulmonary embolization or recurrences. It has been shown that initial treatment with heparin in addition to starting coumarin therapy is crucial to prevent recurrent thromboembolic disease, probably because of the slow onset of action of warfarin. Heparin can be discontinued when a therapeutic INR is obtained (INR between 2.0 and 3.0 for two consecutive measurements) provided that it is given for at least 5 days. The optimal duration of subsequent anticoagulant therapy with warfarin is still uncertain and depends on the individual assessment of risks for recurrent disease and bleeding, but it is recommended for at least 3 months after a first episode of DVT.

Mechanism of Action

Unfractionated heparin (UFH) is the oldest used anticoagulant in the treatment and prevention of thrombotic disease. This compound induces a conformational change in the structure of the natural anticoagulant antithrombin, thus enhancing
the inhibition of in particular thrombin (clotting factor IIa) and activated factor X (clotting factor Xa) (Figure 1). Because of the short half-life of unfractionated heparin, it should be administered by continuous intravenous infusion. Furthermore, due to the wide variability in bioavailability, the optimal dose needs to be monitored daily by measuring the aPTT value (activated partial thromboplastin time). Therefore, treatment with unfractionated heparin requires hospitalization.

Low-molecular weight heparins (LMWH) are extracted from unfractionated heparin by enzymatic or chemical degradation. Relative to UFH, they have an increased anti-factor Xa activity and a less pronounced anti-factor IIa activity. LMWH have a longer plasma half-life and less individual variability in pharmacological activity, which enables the administration of these agents once or twice a day subcutaneously, in a dose that only needs to be adjusted for weight without further laboratory monitoring.

Warfarin, introduced as a rodenticide in the late 1940's, resemble vitamin K in structure and act by inhibition of the synthesis of the vitamin K-dependent clotting factors II, VII, IX and X. The most widely used vitamin K antagonists (warfarin, acenocoumarol and phenprocoumon) are for oral use and differ mostly in plasma half life. The biological effect is variable, both inter- and intraindividually, so frequent laboratory control of the INR for measuring the intensity of anticoagulant action is required.

![Figure 1 Mechanism of action of unfractionated heparin.](image-url)
Low-molecular weight Heparin as Replacement of Unfractionated Heparin

At least 10 clinical studies compared UFH with LMWH for the initial treatment of DVT and showed consistently that LMWH is better with respect to safety and efficacy than UFH. Subsequently, LMWH was used in trials that compared home treatment with inpatient therapy. Simultaneously, two landmark trials were published in 1996. In both studies, not all patients randomised to LMWH were treated entirely outside of hospital; some were discharged after a short period of initial hospitalisation.

In the Koopman et al. study, 6.9 percent of patients with DVT who were treated with LMWH had recurrent thromboembolic disease, compared to 8.6 percent of patients treated with UFH over a period of 6 months of follow-up (difference 1.7%; 95% CI: -3.6 to 6.9). In the Canadian study, the figures were 5.3 percent and 6.7 percent respectively (difference 1.4%; 95% CI -3.0 to 5.7), although the follow-up was limited to 3 months. With regard to safety, no differences in bleeding complications or death were observed between the two strategies. Since then, several prospective cohort studies confirmed that home treatment is safe, effective and feasible for nearly all patients with DVT. In fact, in an ideal situation without any organisational problems, it was calculated that more than 95% of patients with isolated DVT symptoms can be treated at home.

Patient Satisfaction in Home Treatment Protocols

Few studies investigated patient satisfaction of initial home treatment for DVT. Data on quality of life derived from the study by Koopman et al. indicate that (home) treatment with LMWH is associated with less impairment of physical activity and social functioning. Harrison and colleagues found that over 90% of patients treated at home have a high degree of satisfaction and that more than two thirds of the treated population is able to self-inject LMWH.

For the long-term treatment with anticoagulants, patient satisfaction can probably also be increased in the near future, if patients are given more self-control about their treatment. For instance, self-monitoring of oral anticoagulation and self-adjustment of the dose of warfarin has been found to be feasible and as good as doctor’s control, by use of a portable device that measures INR values from capillary blood.
Economic Aspects

By treating patients with DVT in an outpatient setting, a substantial reduction in costs can be achieved\(^\text{15,16}\). For instance, in one of the trials comparing outpatient treatment with LMWH to hospitalised patients treated with UFH, the patients randomised to LMWH were admitted on average for 1.1 days, compared to 6.5 days in the group treated with UFH\(^\text{17}\). In another randomised trial, patients that were treated with UFH were, on average, admitted for more than 12 days, compared to one day for the DVT patients treated with LMWH, which resulted in a cost reduction of up to 40% per patient\(^\text{10}\). Assuming that patients have to be treated for a minimum of five days with low molecular weight heparin and for a minimum of three months with warfarin, and that they would have to be hospitalised for the duration of heparin treatment, Dunn and colleagues estimated a reduction of $1.645 in total health care costs per patient if treated at home\(^\text{17}\).

Although a maximum of 60% in cost reduction is possible, depending on the proportion of patients managed at home, this does not take into account the costs made by home care organisations\(^\text{18}\).

Essential Requirements for Home Treatment

It is necessary to realise that patients who were included in clinical studies do not always have the same characteristics as those seen in daily practice. For instance, patients with an increased risk of bleeding, with renal impairment, or pregnant women were excluded in all trials. Nevertheless, most patients will be eligible for home treatment, especially when it is possible to establish a multidisciplinary clinical service with experience in diagnosing and managing DVT\(^\text{19,20}\).

Regardless of the place of initial treatment, appropriate diagnostic facilities are essential in order to prevent an unnecessary and potentially harmful treatment with anticoagulants. In approximately 70% of patients that present with signs of DVT, venous thrombosis can be ruled out by using appropriate objective diagnostic methods\(^\text{19}\). Compression ultrasonography of the femoral and popliteal

Table 1 Essential requirements for successful home treatment.

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<td>Development of guidelines for selection of patients for home treatment</td>
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<td>Availability of a patient education brochure</td>
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<td>Reliable support in the home setting (spouse, family member, friend)</td>
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<td>Possibility for home-care services</td>
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<td>Around the clock availability of emergency department facilities</td>
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<td>Adequate oral anticoagulant therapy control and follow-up of patients</td>
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Table 2 Relative contraindications for outpatient treatment with LMWH.

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<th>Relative contraindications for outpatient treatment with LMWH</th>
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<td>Concurrent symptomatic pulmonary embolism</td>
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<td>Active bleeding or a known bleeding disorder</td>
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<tr>
<td>Important comorbidity (e.g., severe liver disease or marked renal insufficiency)</td>
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<td>Uncertain compliance or follow-up</td>
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veins is the best evaluated diagnostic method in patients with a suspected first episode of DVT.

For the treatment of patients with uncomplicated DVT outside a hospital, some essential requirements have to be fulfilled (Table 1) 20. First, guidelines for the selection of patients who are eligible for home treatment need to be developed in a multidisciplinary team with both hospital and home care physicians. Relative contraindications for home treatment are listed in Table 2. In general, patients with important comorbidity should be hospitalised. It is important to note that, although patients are traditionally advised to be immobilised in order to prevent immobilisation from a thrombus in the leg, there is no evidence to support this 21. Second, patients need to be informed about the possible complications of DVT and its treatment, ideally by means of a patient education brochure. It is needless to say that the treating physician must be convinced that the patient has understood the impact of the disease and he must be confident about the patients' compliance in treatment and follow-up. Proper instructions (and training) about the injection of LMWH, either by the patient himself, or by others (including family members and nurses in case of availability of home-care services) needs to be provided. In the home setting, reliable support of a spouse or family member, and otherwise home care services, need to be available. Furthermore, a 24 hours service has to be available in case patients develop complications at home. This service can either be given by the local hospital or by home care physicians who are experienced in that field. Finally, control of the anticoagulant level and subsequent dosing adjustments have to be performed adequately by either an anticoagulation clinic or local laboratory.

Conclusion

Subcutaneous LMWH is more effective and safe as adjusted-dose UFH for the treatment of DVT and permits treating the great majority of patients in an outpatient setting.

To ensure successful home treatment of DVT, there are some essential requirements. First, the disease has to be confirmed by objective diagnostic
methods. Then, patients who are suitable for home treatment have to be selected. All patients have to be educated about their disease and possible complications and side effects of treatment. Subsequently, patients have to demonstrate that they are able to inject themselves or there has to be other, reliable, support. Finally, there have to be 24 hour facilities to address complications of DVT or its treatment, and adequate monitoring of anticoagulant therapy needs to be present. Using hospital facilities, home care physicians can play an important role in the treatment of patients with DVT in an outpatient setting. To provide optimal care in different settings, regional home treatment programs should be designed and evaluated.

References