LECTURE

ΔΙΑΛΕΞΗ

Treatment of deep vein thrombosis and pulmonary embolism

The treatment of deep venous thrombosis and pulmonary embolism is reviewed. The treatment, with unfractionated heparin, low molecular weight heparins and oral anticoagulation are presented and discussed. The various therapeutic regimens and the methods of laboratory monitoring are described.

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Θεραπεία της εν τω βάθει φλεβικής θρόμβωσης και της πνευμονικής εμβολής

Περίληψη στο τέλος του άρθρου

Key words

Low-molecular weight heparins
Pulmonary embolism
Unfractionated heparin
Venous thrombosis

1. INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two conditions which are clinical manifestations of the same disease proccess, although patients with PE symptoms have a mean life expectancy shorter than that of patients with DVT symptoms.

Patients who are treated for PE are almost 4 times more likely (1.5% vs 0.4%) to die of recurrent of venous thromboembolism (VTE) in the next year than are patients who are treated for (VTE).[1] Continuous intravenous (IV) unfractionated heparin (UFH) is the standard treatment, which nearly always requires hospitalisation. The use of a low molecular weight heparin (LMWH) has markedly simplified the treatment of carefully selected patients with DVT. Shorter hospital stay or home treatment with a LMWH both decrease the cost of therapy and improve patient's quality of life. Thrombolytic treatment and surgery are restricted to very rare patients with DVT. Thrombolytic therapy is usually indicated for the treatment of patients with acute massive embolism who are hemodynamically unstable and who have no contraindication to this treatment. It should be recognised that thrombolytic therapy is associated with a significantly higher risk of bleeding than heparin-warfarin therapy. Hirudin and Argatroban, two different thrombin inhibitors and Orgaran, an heparinoid compound, are mainly used in patients with heparin induced thrombocytopenia.

2. TREATMENT WITH UFH AND LABORATORY MONITORING

As soon as the diagnosis is objectively documented or during the investigation period if VTE is likely, a bolus of 5,000–7,500 U is given intravenously followed by an IV perfusion with a hourly dose of 1,000–1,500 U aiming at a plasma heparin level of 0.30–0.60 IU/mL with an amidolytic method. The first blood test should be performed around 4 hrs after the beginning of treatment. It has to be emphasized that recent work has shown that the anti-Xa activity of plasma samples may vary when measured with different methods and/or instruments.[2,3] A nomogram such as the one of Cruickshank et al[4] can be used to determine the dosage according to blood tests results. In practice, activated partial thromboplastin time (APTT) is more often used than anti-Xa measurement. APTT results may vary according to the reagent used and no system such as the INR expression has been made available. Usually, the treatment with a continuous infusion of UFH aims to an APTT ratio ranging between 2–3 or 1.5–2.5, according to different authors and the instruments and reagents used. The heparin nomogram for daily practice will depend on the locally used APTT. Monitoring of platelet count before treatment and every 3–4 days during treatment is recommended in order to reduce the risk of heparin induced thrombocytopenia.

3. TREATMENT WITH A LMWH AND LABORATORY MONITORING

When LMWH is used there are two different modalities for the administration of the drug: either the whole daily dose is given in one single subcutaneous (sc) injection of about 175–200 anti-Xa IU/kg body weight or in two injections a day at a dose of about 100 anti-Xa IU/kg for each injection. There is no clear difference in the clinical results of both protocols regarding their relative efficacy and safety. It should be noted that there is some suggestion from pharmacokinetics studies that accumulation of the LMWH is more frequently observed in the latter protocol rather than in the former one.

LMHWs have been administered without monitoring since no clear evidence of a relation between efficacy and safety results and anti-Xa plasma level is available. However, it is being more and more recognised that monitoring anti-Xa activity is indicated in special categories of patients such as patients with renal disease in whom the plasma clearance of the drug is reduced. Patients with a creatinine clearance lower than 30 mL/min should preferably receive subcutaneous unfractionated heparin than a LMWH.

Other groups of patients in whom laboratory monitoring of anti-Xa activity may be indicated are pregnant women and infants, patients with a high bleeding risk, patients with a body weight lower than 50 or higher than 90 kg and patients receiving a prolonged treatment (longer than 5–6 days). Adjusted versus fixed dose of LMWHs may be preferable in these categories of patients.

There is some evidence from TIMI IIA trial that at high LMWH doses, such as more than 100 anti-Xa 10/kg every 12 hours, a relationship between anti-Xa activity and minor and major bleeding does exist, even in patients in whom no invasive procedure has been used[5] (tabl. 1). The LMWHs have a clear advantage over UFH. They can be used for an outpatient management. Home treatment is now a reality since the controlled trials of Koopman et al[6] and of Levine et al.[7]

The rate of recurrences of VTE, major hemorrhage and that of mortality are reduced as compared to those obtained with UFH. Oral anticoagulant was started on the first day of LMWH treatment. In some patients with severe proximal DVT the beginning of oral anticoagulant can be postponed until day 5 or 6 as noticed in the American College of Chest Physicians (ACCP) recommendations.[1]

The most important problem is the observance of the precautions to be taken before allowing a home anticoagulant treatment.[8] Home treatment is restricted to well selected patients, it is cost saving and improves quality of life. Minimal elements for early discharge or outpatient therapy are gathered in table 2.[9] The treating physician should make this decision and should be in close contact with the patient's practitioner. Simplification of treatment does not mean trivialisation.

Table 1. Results of TIMI IIA trial.

Lovenox dose	1.25 mg/kgX2	1.0 mg/kgX2	P
Patients (n)	321	309	
Anti-Xa activity peak and (range)	1.6 (1.1–1.8)	1.1 (1.0–1.2)	<0.05
Anti-Xa activity peak and (range)	1.8 (1.6–2.1)	1.2 (1.2–1.9)	
In patients with major hemorrhage*	n=21	n=6	0.004

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* At instrumental sites major hemorrhage in 17 and 5, respectively P=0.01

4. DURATION OF ORAL ANTICOAGULATION

The duration of oral anticoagulant treatment is still a matter of debate. It is clear that the duration after a first episode of VTE may differ in patients with or without a precipitating risk factor and the presence or absence of hereditary or acquired thrombophilia. In patients with an idiopathic episode the duration of treatment should not be shorter than 6 months.[10] Patients with reversible or time-limited risk factors should be treated for 3–6 months. The duration in patients with thrombophilia (hereditary) should be decided case by case taking into consideration the usual greater severity of the clinical expression of antithrombin (AT), protein C (PC) and protein S (PS) deficiency as compared to FV or FII mutation.

In patients with recurrent episodes long term anticoagulation is frequently required. In some patients who have a contra-indication or a resistance to oral anticoagulant therapy, the treatment with LMWH should be continued. However, there is no recommended dose and many authors will not reduce the usual dose administered during treatment at least for the first six weeks after beginning heparin administration. A lower dose, half this dose for instance, may be used after this period for at least 6 weeks. There is no clear recommendation related to the most appropriate strategy.

Table 2. Minimal elements for early discharge or outpatient therapy.

Responsible physician must assure the following:
Stable patient with normal vital signs
Low bleeding risk
Absence of severe renal insufficiency
Practical system for administration of LMW-heparin and warfarin with appropriate monitoring
Practical system for surveillance and treatment of recurrent VTE and bleeding complications

5. ALTERNATIVE TREATMENT STRATEGIES

Theoretically, thrombolytic therapy should be preferred to anticoagulant treatment in patients with DVT, since the later does not induce lysis of the thrombus. An effective thrombolytic treatment may prevent the postphlebitic syndrome. However, the risk of severe bleeding is at least twice as important as that of heparin. This thrombolytic therapy is restricted to very special cases of proximal extended DVT.

In patients with PE causing cardiogenic shock or overt hemodynamic instability, thrombolytic treatment is used if there is no contraindication. Streptokinase (SK) and urokinase (UK) are less often used rather than rt-PA.

A limited use of the inferior vena cava filters was recommended in the 5th North American Consensus Conference[1] which paid attention to the results of the recent study of Decousus et al.[11] In this work, the rate of recurrent DVT was significantly higher (20.8%) in patients followed up during 2 years as compared to the results observed in the control population (11.6%). Finally, a non permanent filter has been used in few groups of patients. The consensus recommendations of the NACC of 1998 and 2000 are similar. Surgery may be indicated in patients with acute DVT and is mainly limited to some patients with coerulea alba dolens.

Finally, cost effectiveness of anticoagulant therapy in DVT deserves great attention. However, modern treatment and specially ambulatory treatment is clearly more cost effective as compared to traditional treatment.[12]

ΠΕΡΙΛΗΨΗ

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Ανασκόπηση της θεραπείας της εν τω βάθει φλεβικής θρόμβωσης και της πνευμονικής εμβολής. Προτείνονται θεραπευτικά σχήματα, με χορήγηση κλασικής ηπαρίνης, ηπαρινών χαμηλού μοριακού βάρους και αντιπηκτικών από το στόμα, καθώς και ο εργαστηριακός έλεγχος για τη ρύθμισή τους. Επίσης, συζητούνται άλλες θεραπευτικές στρατηγικές συμπεριλαμβανομένης της θρομβόλυσης.

Λέξεις ευρετηρίου: Ηπαρίνες χαμηλού μοριακού βάρους, Ηπαρίνη, Πνευμονική εμβολή, Φλεβική θρόμβωση

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