Breathing Life Into
Pulmonary Embolism

In the absence of a cardiogenic shock or overt hemodynamic instability, unfractionated heparin (UH) is the standard treatment for patients affected by PE. What other treatments are available to deal with this common pathologic condition?

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Pulmonary embolism (PE) is a relatively common pathologic condition that affects apparently healthy individuals, as well as medical or surgical patients. In most cases, antithrombotic treatment of PE is the same as for deep vein thrombosis (DVT). In fact, PE and DVT are considered as part of a spectrum of a single disease defined as venous thromboembolism (VTE), because of their identical pathophysiology and risk factors, and identical therapeutic goals. It has been observed that approximately 30% of apparently isolated episodes of PE are associated with silent DVT[1], and that silent PE can be detected in 40% to 50% of patients affected by DVT.[2] Common therapeutic objectives are the prevention of thrombus extension and embolism, and the prevention of recurrent episodes of VTE to reduce the risk of fatality.

About 30% of apparently isolated episodes of PE are associated with silent DVT.

What are the treatments?

In the absence of a cardiogenic shock or overt hemodynamic instability, unfractionated heparin (UH) is the standard treatment for patients affected by PE. The subsequent development of low molecular weight heparins (LMWH), with pharmacologic and pharmacokinetic advantages over their parent compound, opened a new era in the management of VTE. Strong evidence first came from the results of several randomized clinical trials that compared LMWH with UH in the initial treatment of acute proximal DVT. A number of meta-analyses showed that LMWH are at least as safe and effective as UH.[1,2] The practical advantages of the LMWH together with a better understanding of the pathophysiology of VTE as a single disease, have subsequently introduced the possibility of treating patients with hemodynamically stable PE with the newer compounds. The results of two clinical trials published in 1997 (the Columbus study, conducted on patients presenting with VTE including submassive PE, and the Thésée study, specifically addressed to patients with submassive PE[3,4]) and a third, more recent trial (conducted on patients admitted for DVT, who also had objectively documented PE) clearly prove that LMWH are at least as safe and effective as UH also for the treatment of submassive PE (Table 1).[5]

What is the feasibility of outpatient treatment of PE?

As a result of the excellent findings from clinical trials with LMWH, and because the LMWH can be given subcutaneously without need for laboratory monitoring, there has been widespread and growing interest in outpatient treatment of VTE. Positive

experiences have been accumulated worldwide in the management of DVT patients. Evidence from reports on clinical practice support the possibility of safely extending the home treatment program to patients with PE.[6,7] In a Canadian study, 51.3% of patients presenting with hemodynamically stable PE were entirely treated at home, and 17.1% were hospitalized for an average of just 2.5 days.[7] The rate of events were comparable to those expected among fully hospitalized patients. However, it should be recommended to limit outpatient treatment of VTE, and in particular of PE, only to selected and well experienced hospital-based centres.

The latest guidelines on antithrombotic therapy of the American College of Chest Physicians recommend LMWH as the first option for patients in the acute stage of VTE. Dosages of antithrombotic treatment are the same for both DVT and PE patients.[8] It is also recommended that outpatient therapy of stable PE with LMWH regimens can be prescribed to all patients with:

- normal vital signs,
- low risk for bleeding,
- absence of severe renal insufficiency,
- availability of a practical system for administering LMWH and oral anticoagulants with appropriate monitoring; and
- the availability of a practical system for surveillance and treatment of recurrent VTE and bleeding complications.

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Why use thrombolytic agents?

Thrombolysis has been shown to be life-saving when administered to patients with PE causing cardiogenic shock or overt hemodynamic instability.[8] Thrombolytic agents have a number of potential advantages over anticoagulants, but expose patients to a greater risk of bleeding. Advantages include:

- lysis of the thrombi,
- restoration of the venous circulation to normal; and
- reduction in damage to the venous valves, thus reducing the risk of venous hypertension.

Right ventricular dysfunction is an important warning of a possible adverse outcome. As such, ongoing studies are evaluating the role of thrombolytic treatment in patients presenting with submassive pulmonary embolism, but with concomitant echocardiographic signs of right ventricular dysfunction. The thrombolytic agent alteplase in combination with UH was recently shown to improve the clinical course of such patients as compared to UH alone without increasing the risk of bleeding.[9]

What are the long-term treatments of PE?

Oral anticoagulant treatment is effective in the prevention of recurrent DVT extension, or PE. Treatment should be started on the same day as UH or LMWH and administered in combination until the therapeutic range (for most patients international normalized ratio between 2.0 and 3.0) is

achieved and maintained for at least two consecutive days.[8]

The optimal duration of anticoagulant therapy for DVT and PE is still a matter of intense debate. The incidence of recurrent events is low when VTE is provoked by a transient risk factor (*i.e.*, surgery, trauma, immobilization, oral contraceptives) and is very high when the risk factor is permanent (*i.e.*, congenital or acquired thrombophilia, cancer). Unfortunately, there is still a large proportion of patients in whom the cause of VTE remains unidentified. The results of prospective studies specifically addressed on the duration of anticoagulant therapy[10-12] have shown that a substantial proportion of patients with idiopathic DVT do have recurrent episodes of VTE after oral anticoagulant treatment is stopped (approximately 7% to 10% per year), regardless of the duration of the treatment. Similar findings were observed after a first episode of idiopathic PE.[13] Currently, prolonged treatment is indicated for patients with active cancer, antithrombin deficiency, and antiphospholipid antibody syndrome. It is recommended to treat patients with idiopathic VTE for six months and patients with transient risk factors for three months.[8] Finally, patients with recurrent VTE should be treated indefinitely.[8] *PCard*

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Table 1

Recommended doses of the antithrombotic agents

Low molecular weight heparin

- Dalteparin calcium, 200 anti-Xa IU/Kg subcutaneously (SC) every 24 hours
- Enoxaparin sodium, 1 mg/Kg SC every 12 hours
- Nadroparin calcium, 86 anti-Xa IU/Kg SC every 12 hours
- Tinzaparin sodium, 175 anti-Xa IU/Kg SC every 24 hours
- Stop after at least 5 days when INR >2.0 for 2 consecutive days

Unfractionated heparin

- Start with a bolus of 80 IU/Kg followed by intravenous infusion of approximately 18 IU/Kg aiming at therapeutic levels of the activated partial thromboplastin time of 1.5 to 2.5 control
- Stop after at least 5 days when INR >2.0 for 2 consecutive days

Warfarin

- Start with 5 mg and adjust dosage aiming at therapeutic INR levels of 2.0 to 3.0

Thrombolytic agents

- Alteplase, 100 mg administered in a 10 mg bolus followed by 90 mg intravenous infusion over a period of 2 hours

INR: international normalized ratio

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Take-home message

- PE is a relatively common pathologic condition that affects apparently healthy individuals, as well as medical or surgical patients.
- Unfractionated heparin (UH) is the standard treatment for patients affected by PE.
- Low molecular weight heparins (LMWH) opened a new era in the management of VTE.

Net Readings

1. EMedicine.com:
   www.emedicine.com/EMERG/topic490.htm
2. MedlinePlus:
   www.nlm.nih.gov/medlineplus/pulmonaryembolism.html

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