Diagnosis and Treatment of Deep Vein Thrombosis

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Deep vein thrombosis and pulmonary embolism are important clinical disorders that affect patients in many medical and surgical specialties. In North America, deep vein thrombosis results in hospitalization of up to 600,000 patients per year. Pulmonary embolism is also a serious problem that occurs in more than 500,000 patients per year, of whom approximately 200,000 will die. Almost half of those patients who die will be terminally ill or suffer an incurable disease, but the remainder of the deaths occur in patients who otherwise could have recovered completely.[1]

DIAGNOSIS OF VENOUS THROMBOEMBOLISM

The clinical diagnosis of both venous thrombosis and pulmonary embolism is inaccurate because of the insensitivity and nonspecificity of the findings. Invasive, objective tests for venous thrombosis and pulmonary embolism such as ascending venography and pulmonary angiography are the reference standards for diagnosis, but they are not always easy to perform and they cannot be used for a considerable number of very ill patients. There is, therefore, an increasing trend toward using noninvasive methods either alone or in combination for the diagnosis of venous thromboembolism.[2] These methods entail less risk, can be performed more quickly and conveniently, and are usually more cost-effective.

It is important that the diagnosis of deep vein thrombosis is accurate because a falsely negative diagnosis will increase the risk of pulmonary embolism and the postphlebitic syndrome in the untreated patients, whereas a falsely positive diagnosis will unnecessarily expose the patient to the side-effects of anticoagulant treatment and to the inconvenience of hospitalization. The clinical diagnosis of deep vein thrombosis has a low sensitivity and specificity and, therefore, is unreliable. Less than 50% of patients who present with classical symptoms and signs have deep vein thrombosis confirmed by objective tests.[3] The exception is in patients with clinical features typical of phlegmasia cerulea dolens which is almost always caused by extensive iliofemoral thrombosis. Conversely, some patients have extensive deep vein thrombosis which is clinically silent and are at risk of serious morbidity or mortality. Ascending venography is the standard for diagnosing venous thrombosis. However, it is difficult to perform, requires considerable experience to execute and to interpret the results adequately. The noninvasive tests for venous thrombosis include impedance plethysmography, B-mode ultrasonography and Doppler ultrasonography. Impedance plethysmography (IPG) detects volume changes in the leg which are reduced by venous obstruction, usually by deep vein thrombosis involving the popliteal or proximal veins. In symptomatic patients, the sensitivity and specificity of IPG for the diagnosis of DVT are 94% and 95% respectively.[4] B-mode ultrasonography assesses the common femoral, superficial femoral, and popliteal veins using compressibility as the main criterion for the diagnosis of deep vein thrombosis. The pooled sensitivity and specificity of B-mode ultrasound from many studies are 97% and 98% respectively.[5] Doppler ultrasonography is a convenient, rapid, and less expensive method which detects alteration in venous flow but interpretation of the tests is highly subjective and requires great skill.[6] Other less common techniques used to diagnose venous thrombosis include strain gauge plethysmography and tests of thrombin formation and fibrinolysis. Of the noninvasive tests, impedance plethysmography and B-mode ultrasound are the most practical and have been shown to be clinically useful in the management of patients with suspected DVT.[7,8]

The signs and symptoms of pulmonary embolism can be caused by other cardiorespiratory disorders and thus the clinical diagnosis is nonspecific. Pulmonary

angiography is the standard test for establishing pulmonary embolism, although many severely ill patients cannot undergo the test. Arterial blood gases, chest X-ray, and ECG findings are all nonspecific. The most commonly used noninvasive test is isotope lung scanning.[9] A normal perfusion lung scan excludes a diagnosis of pulmonary embolism and scan with a large ventilation/perfusion mismatch is diagnostic. Other lung scan findings are not conclusive of pulmonary embolism. A practical approach to the diagnosis of pulmonary embolism include a chest X-ray and electrocardiogram, followed by perfusion lung scanning. A negative perfusion lung scan rules out pulmonary embolism. If, however, the perfusion scan is positive, a ventilation scan should be done. A ventilation/perfusion mismatch involving one or more lung segments markedly increases the probability of pulmonary embolism and therapy should be given for most patients.[10,11] However, a ventilation/perfusion match should be further tested by venography, impedance plethysmography, or pulmonary angiography. If the tests for venous thrombosis confirm deep vein thrombosis, antithrombotic therapy should be started. If venography is negative, pulmonary angiography should be performed to confirm the diagnosis.

MANAGEMENT OF VENOUS THROMBOEMBOLISM

Heparin is the treatment of choice in the initial management of venous thromboembolism. Heparin has a number of limitations that are related to its pharmacokinetic, antihemostatic, and biophysical properties.[12] Heparin binds to plasma proteins which compete with its binding to antithrombin III and contributes to the variability in the dose response to heparin and to the phenonemon of heparin resistance. In addition, heparin binds to endothelial cells and macrophages which is responsible for its dose-dependent mechanism of clearance. Thrombin bound to fibrin and factor Xa in the prothrombin complex on the platelet surfaces are relatively resistant to inactivation by the combination of heparin and antithrombin III. In addition to its effects on coagulation, heparin binds to platelets and inhibits their function, thus contributing to the hemorrhagic side-effects of heparin. To overcome the limitations of heparin, unfractionated heparin, which contains glycosaminoglycans of various molecular weights ranging from 2000 to 30,000, has been fractionated into various components. The component with a molecular weight ranging from 4500 to 5000, the low molecular weight fraction, has pharmacological and pharmacokinetic advantages over the parent compound which result in its having potential for greater efficacy and safety.[13] Low molecular weight heparins exhibit less binding of plasma proteins and endothelial cells and therefore do not share the pharmacokinetic limitations of heparin. As a result, low molecular weight heparins have a much more predictable dose response and a dose-dependent mechanism of clearance along with a longer plasma half-life than heparin. In addition, low molecular heparins bind less to platelets and produce less microvascular bleeding with an equivalent antithrombotic effect in experimental animals.

Prophylaxis

Venous thromboembolism is a common complication in surgical patients. In the absence of prophylaxis, patients undergoing major general surgery have a 10% to 40% incidence of calf vein thrombosis, a 2% to 8% incidence of proximal vein thrombosis, and a 0.1% to 0.8% incidence of fatal pulmonary embolism. Patients undergoing orthopaedic procedures and who do not receive prophylaxis are at high risk for venous thromboembolism; in this group 40% to 80% develop calf vein thrombosis, 10% to 20% develop proximal vein thrombosis, and 1% to 5% suffer fatal pulmonary embolism.[14] Thus, the morbidity and mortality of thromboembolic disease is a major problem in hospitalized patients.

A number of Consensus Conferences[14,15,16] have defined risk categories among patient groups based on clinical criteria (Table 1), and the rates of venous thromboembolism within the categories (Table 2) and have made recommendations for the use of thrombosis prophylaxis. Several methods of thrombosis prophylaxis have been evaluated including low-dose standard heparin, adjusted-dose standard heparin, oral anticoagulants, antiplatelet drugs, intermittent pneumatic compression devices, and low molecular weight heparins. Low-dose heparin prophylaxis is a commonly recommended and utilized form of prophylaxis for moderate and high-risk patients. In a recent meta-analysis,[17] low-dose heparin was shown to be effective in reducing the risk of venous thrombosis in general surgical patients, in orthopaedic patients, and in patients undergoing urological procedures with a risk reduction in each category of approximately 65%. Low molecular weight heparins have recently been evaluated for

Table 1. Clinical risk categories for deep vein thrombosis
(Thrift, Brit Med J 1992;305:567)

LOW RISK GROUPS	Minor surgery (<30 min); no risk factors other than age Major surgery (>30 min); age <40, no other risk factors Minor trauma or medical illness
MODERATE RISK GROUPS	Major general, urological, gynecological, cardiothoracic, vascular, or neurological surgery; age ≥40 years or other risk factor Major medical illness: heart or lung disease, cancer, inflammatory bowel disease Major trauma or burns Minor surgery, trauma, or illness in patients with previous deep vein thrombosis pulmonary embolism, or thrombophilia
HIGH RISK GROUPS	Fracture or major orthopaedic surgery of pelvis, hip, or lower limb Major pelvic or abdominal surgery for cancer Major surgery, trauma or illness in patients with previous deep vein thrombosis, pulmonary embolism or thrombophilia Lower limb paralysis (for example, hemiplegic stroke, paraplegia) Major lower limb amputat

Table 2. Frequency of DVT in clinical risk categories
(Thrift, Brit Med J 1992;305:567)

	DEEP VEIN THROMBOSIS	PROXIMAL VEIN THROMBOSIS	FATAL PULMONARY EMBOLISM
LOW RISK	<10%	<1%	0.01%
MODERATE RISK	10-40%	1-10%	0.1-1%
HIGH RISK	40-80%	10-30%	1-10%

the prevention of venous thromboembolism in randomized clinical trials in general surgical patients, in orthopaedic patients, in spinal cord injured patients, and in medical patients.[18,19] The data from the general surgical studies demonstrate that low molecular weight heparins are effective in preventing deep vein thrombosis, and in doses that give an equivalent antithrombotic effect to standard unfractionated heparin, the risk of bleeding complications is much less. Thus, the relative safety and efficacy favors low molecular weight heparin over unfractionated heparin in these patients. Patients undergoing orthopaedic procedures provide a much more rigorous test of the efficacy and safety of low molecular weight heparin fractions in deep vein thrombosis prevention. Before the introduction of low molecular weight heparins, a number of methods of thrombosis prophylaxis were evaluated in patients undergoing orthopaedic procedures but none was ideal.[20,21] Low-dose heparin given subcutaneously is only 50% effective, aspirin has been shown to be of no benefit when venography is used to detect venous thrombosis, and dextran which provides about a 50% risk reduction is not widely used because of the frequency of side-effects including heart failure or allergic reactions. Oral anticoagulants which are widely used but require careful monitoring, result in an approximately 60% risk reduction in venous thrombosis. There have been several studies of low molecular weight heparin in patients undergoing elective and emergency orthopaedic procedures which have demonstrated their safety and efficacy.[18,19] The absolute rates of thrombosis in randomized trials in patients undergoing total hip replacement are shown in Table 3.[20] In a recent meta-analysis[18] in studies comparing low molecular weight heparin with heparin in general surgical and orthopaedic patients (Table 4), low molecular weight heparins have been shown to be either as effective or superior in the prevention of deep vein thrombosis as compared with the parent compound without an increased risk of bleeding. Thus, there is solid evidence from randomized clinical trials that low molecular weight heparins are highly effective in the prevention of deep vein thrombosis in high-risk surgical patients.

Table 3. DVT prophylaxis in elective hip surgery A meta-analysis

(Mohr et al., Arch Intern Med 1993;153:2221)

	STUDIES	PATIENTS	DVT%	PROX DVT
NO TREATMENT	6	395	50	24
ASPIRIN	3	135	47	—
GRADUATED COMPRESSION	3	152	39	9
DEXTRAN	3	190	30	9
LD HEPARIN	5	511	24	10
INT PNEUM COMPRESSION	4	283	22	15
WARFARIN	3	139	19	7
ADJ HEPARIN	2	88	17	9
LMW HEPARIN	6	541	12	4

Table 4. A meta-analysis of DVT prophylaxis with lmw heparin

(Nurmohamed et al., Lancet 1992;340:152-156)

	LMW HEPARIN vs HEPARIN	
DEEP VEIN THROMBOSIS	**RELATIVE RISK**	**95% CI**
ALL SURGERY	0.74	0.65 - 0.86
GENERAL SURGERY	0.79	0.65 - 0.95
ORTHOPAEDIC SURGERY	0.68	0.54 - 0.86
PULMONARY EMBOLISM		
ALL SURGERY	0.43	0.26 - 0.72
GENERAL SURGERY	0.44	0.21 - 0.95
ORTHOPAEDIC SURGERY	0.43	0.22 - 0.82
MAJOR BLEEDING		
ALL SURGERY	0.98	0.69 - 1.40
GENERAL SURGERY	1.01	0.70 - 1.48
ORTHOPAEDIC SURGERY	0.75	0.26 - 2.14

Treatment of Deep Vein Thrombosis and Pulmonary Embolism

Anticoagulant therapy is the standard treatment in patients with venous thromboembolism. Heparin may be administered by intravenous infusion, intermittent intravenous injection, or by subcutaneous injection. Each method of administration of heparin is effective,[22] but there is evidence that intermittent intravenous injections are associated with greater frequency of bleeding complications. Heparin should be administered in doses which are sufficient to prolong the results of appropriate tests of blood coagulation to within a defined level. A practical method of monitoring heparin therapy is the activated partial thromboplastin time which should be prolonged to 1½ to 2½ times the control level.[23] Initial heparin treatment should be followed with secondary prophylaxis with warfarin for 3 to 6 months at a dose to give an International Normalized Ratio (INR) of 2.0 to 3.0.[24] Heparin is effective in reducing recurrent venous thromboembolism in patients with deep vein thrombosis and death in patients with pulmonary embolism.[25]

Recently the low molecular weight derivatives of heparin have become available for treatment of venous thrombosis. Two characteristics make these agents excellent candidates for the treatment

Table 5. Treatment of DVT with low molecular weight heparins: a meta-analysis (Lensing et al., Arch Intern Med 1995;155:601)

	LMWH	HEPARIN	RR (95% CI)	P
Recurrent Venous Thromboembolism	17/540 (3.1%)	38/546 (6.6%)	53% (18% - 73%)	<0.01
Major Bleeding	6/753 (0.8%)	21/759 (2.8%)	71% (31% - 85%)	<0.005
Mortality	21/540 (3.9%)	39/546 (7.1%)	45% (10% - 69%)	<0.04

of venous thromboembolism: (1) their kinetics are more predictable than those of standard heparin, and (2) their elimination half-life is longer when compared to standard heparin. These properties make weight-adjusted fixed-dose subcutaneous administration of low molecular weight heparin possible in the initial treatment of venous thromboembolism. Many randomized studies have shown that in patients with deep vein thrombosis, low molecular weight heparin treatment either intravenously with dose adjustments or subcutaneously in fixed doses is at least as effective and probably more effective than continuous intravenous adjusted-dose unfractionated heparin demonstrated by increased lysis of the thrombus on repeat venography or by reduction in the size of perfusion defects on lung-scanning.[26,27] The results of two meta-analyses of the studies comparing fixed dose subcutaneous low molecular weight heparin with adjusted-dose standard heparin are shown in Tables 5 and 6.[26,27] Recently, two large trials[28,29] assessed major clinical endpoints during long-term follow up after treatment with either unfractionated heparin or fixed-dose subcutaneous low molecular weight heparin, and both studies reported a lower incidence of recurrent venous thromboembolism and major bleeding complications in patients randomized to low molecular weight heparin. In addition, both trials reported a lower mortality due to causes unrelated to venous thromboembolism in the patients treated with low molecular weight heparin. Whether or not this observation is causally related to the treatment is unknown. A potential development, made possible by the use of a fixed-dose subcutaneous low molecular weight heparin, is home treatment for patients with deep vein thrombosis who are not severely ill. However, before this approach is adopted for routine use, its safety and efficacy should be demonstrated in randomized trials. Low molecular weight heparins have not been formally evaluated in treatment of patients with pulmonary embolism in large trials.

Table 6. Treatment of venous thrombosis with low molecular weight heparin: a meta-analysis (Leizorovicz et al., BMJ 1994;309:299)

	ODDS RATIO	95% CI	p
RECURRENT VTE	0.66	0.41-1.07	0.09
THROMBUS EXTENSION	0.51	0.32-0.83	0.006
MORTALITY	0.72	0.46-1.40	0.16
MAJOR HEMORRHAGE	0.65	0.36-1.16	0.15

Although anticoagulant therapy is highly effective in the management of acute deep venous thromboembolism, it does not produce significant thrombolysis and hence may not reduce the frequency or severity of the postphlebitic syndrome or the long-term sequelae of pulmonary embolism. There is evidence that as many as two-thirds of patients with deep vein thrombosis treated with heparin have residual thrombi with loss of venous valve function and alteration in venous return and more than half of all patients with proximal venous thrombosis will develop symptoms of chronic venous insufficiency. Thrombolytic therapy has a number of potential advantages over anticoagulant therapy which include lysis of thrombi with restoration of the circulation to normal and reduction or prevention of venous valve damage and therefore potential for preventing the postphlebitic syndrome.[30] In pulmonary embolism, thrombolysis may result in complete lysis of the emboli thus improving long-term functional outcome. Streptokinase, urokinase and tissue plasminogen activator have been approved for treatment and are indicated in patients with proximal thrombi, particularly in younger individuals, and in patients with massive pulmonary embolism who do not respond to standard treatment. However, the long-term benefits of thrombolytic therapy in venous thromboembolic diseases have not been demonstrated in randomized trials. STI

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