THE ROLE OF THROMBOLYTIC THERAPY IN TREATMENT OF LOWER EXTREMITY DEEP VENOUS THROMBOSIS

Thesis

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ABSTRACT

The prevention of PE, the restoration of normal venous circulation, the preservation of venous valvular function, and the prevention of postphlebitic syndrome.Thrombolytic therapy does not prevent clot propagation, rethrombosis, or subsequent embolization. Heparin therapy and oral anticoagulant therapy must always follow a course of thrombolysis

KEY WORDS

ROLE

LOWER

THROMBOSIS

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LIST OF ABBREVIATIONS

Abbrev.	Meaning
ALT	Alanine aminotrans-ferase
APTT	Activated partial thromboplastin time
AT III	Anti-thrombin III
CCTVPA	Combined computerized tomographic venography and pulmonary arteriography
CTPA	Computeized tomographic pulmonary arteriography
CVI	Chronic venous insufficiency
DIC	Disseminated intravascular coagulation
DVT	Deep Vein Thrombosis
ELISA	Enzyme-linked immunosorbent assay
HIT	Heparin-induced thrombocytopenia
INR	International normalized ratio
IVC	Inferior vena cava
LMWHs	Low-molecular-weight heparins
MRV	Magnetic resonance venography,
NAP-2	Neutrophil acting peptide 2
NSAIDs	Non-steroidal anti-inflamatory drugs
PE	Pulmonary embolism
OCP	Oral contraceptive pills
PTS	Post thrombotic syndrome
SLE	Systemic lupus erthematosis
SK	Streptokinase
T-PA	Tissue plasminogen activator
UFH	Unfractionated heparin
UK	Urokinase
VTE	Venous thrombo embolism
vWF	Von willberand factor

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Chapter I

INTRODUCTION

In hospitalized patients, the incidence of venous thrombosis is considerably higher and varies from 20-40%. Venous ulceration and venous insufficiency of the lower leg, which are long-term complications of deep venous thrombosis (DVT), affect 0.5% of the entire population. Death from DVT is attributed to massive pulmonary embolism (PE), which causes 200,000 deaths annually in the United States in-hospital mortality.[1]

The natural history of ileofemoral vein DVT is different than isolated femoral-popliteal DVT. In the latter group, recanalization and collateral venous blood flow limit the degree of post thrombotic syndrome (PTS). However, in the iliac veins, adequate recanalization is unlikely and collateral venous blood flow is minimal. This leads to persistent venous outflow obstruction and an increased risk of PTS.[1]

Long-term studies of patients with ileofemoral DVT reported a 44% incidence of venous claudication at 5-year follow-up with standard anticoagulant therapy alone. Furthermore, the rate of recurrence of DVT is twice as high in patients with an ileofemoral DVT than in those with more distal, femoral-popliteal DVT. [2]

Anticoagulation remains the mainstay of the initial treatment for DVT. Heparin prevents extension of the thrombus and has been shown to significantly reduce (but not eliminate) the incidence of fatal and nonfatal pulmonary emboli as well as recurrent thrombosis. Heparin has no effect on preexisting nonadherent thrombus.Heparin does not affect the size of existing thrombus and has no intrinsic thrombolytic activity. [3]

Heparin therapy has little effect on the risk of developing the postphlebitic syndrome. The original thrombus causes venous valvular incompetence and altered venous return leading to a high incidence of chronic venous insufficiency and postphlebitic syndrome. (3)

Thrombolytic therapy offers significant advantages over conventional anticoagulant therapy including the prompt resolution of symptoms, the prevention of PE, the restoration of normal venous circulation, the preservation of venous valvular function, and the prevention of postphlebitic syndrome.Thrombolytic therapy does not prevent clot propagation, rethrombosis, or subsequent embolization. Heparin therapy and oral anticoagulant therapy must always follow a course of thrombolysis. (3)

Venous thrombi in the legs are often large and associated with complete venous occlusion. The thrombolytic agent that acts on the surface of the clot may not be able to penetrate and lyse the entire thrombus. Nevertheless, the data from many published studies indicate that thrombolytic therapy is more effective than heparin in achieving vein patency. (4)

The degree of lysis observed on post treatment duplex is predictive of future venous valvular insufficiency and late (5-10 y) development of postphlebitic syndrome. Preliminary evidence suggests that thrombolytic therapy reduces but unfortunately does not entirely eliminate the incidence of postphlebitic syndrome at 3 years. (4)

The hemorrhagic complications of thrombolytic therapy are formidable (3 times higher) than heparin treatment, and include the small but potentially fatal risk of intracerebral hemorrhage. The uncertainty regarding thrombolytic therapy is likely to continue. (4)

Currently, the American College of Chest Physicians (ACCP) consensus guidelines recommend thrombolytic therapy only for patients with massive ileofemoral vein thrombosis associated with limb ischemia or vascular compromise. [5]

AIM OF THE WORK

Objectives of the study were:

The aim of this study was evaluation of the efficacy of the thrombolytic therapy (streptokinase) in the management of acute ileofemoral DVT versus standard anticoagulant therapy alone as regards:

- Early recanalization of deep venous system.
- Progression of the DVT to pulmonary embolism.
- Major complication between two groups.

Chapter I
PATHOPHYSIOLOGY OF VENOUS DISEASE

Deep vein thrombosis (DVT) occurs when a thrombus, formed from elements of the blood, develops in the deep veins of the lower extremity. Since many patients with acute DVT are asymptomatic, the true prevalence of DVT in the population is unknown. (1)

Furthermore, many studies have relied on the clinical diagnosis of DVT so the actual prevalence of DVT even in hospitalized patients is underestimated. Some have suggested at least 2-3% of the population have experienced a DVT at some time in their life. This chapter will review the causes of acute DVT, and relate the acute pathophysiology of thrombus formation within the venous system to the clinical state.(2)

Deep venous thrombosis and pulmonary embolus represent the early manifestations of thrombus formation in the venous system, while venous stasis disease is late sequelae of acute DVT. The venous hemodynamics in normal limbs will be contrasted with the circulatory changes in limbs with venous stasis disease or chronic venous insufficiency (CVI). In addition, microcirculatory alterations in CVI, an area of new intense focus, will be reviewed. (3)

Etiology of venous thrombosis

The process of thrombosis is a complex interaction of many factors involving the blood and the vessel wall. The coagulation proteins, in concert with their activators and inhibitors, platelet activation, adherence and recruitment, and endothelial cell modulation, play an important, intertwining

role in thrombus formation. In addition, the fibrinolytic system restrains the growth of the thrombus. Despite major advances in coagulation research, the basic etiologic factors in venous thrombosis can still be categorized by Virchow's triad originally described in 1856: (i) stasis of blood flow; (ii) injury to the vessel wall; and (iii) hypercoagulable blood. (4)

Formation of venous thrombosis usually begins in the valve cusp sinuses where eddy currents under phasic flow produce relative stasis. Lowered venous blood flow combined with a hypercoagulable state or local injury initiates thrombus formation composed mainly of fibrin and red blood cells.(5)

1- Thrombus formation

Ultimate formation of a fibrin clot is accomplished by a series of integrated reactions between the blood and the vessel wall. The intrinsic pathway is activated when blood contacts a nonendothelial surface. The foreign surface interacts with factor XII, resulting in activated factor XII (XIIa). Factor XIIa then activates factor XI, a reaction that is calcium dependent. Factor XIa next activates factor IX in the presence of factor VIII, and phospholipid activates factor X. This last reaction is greatly magnified if factor VIII has been exposed to thrombin or factor Xa. (6)

The extrinsic pathway is initiated by tissue thromboplastins released by injured cells. These phospholipoproteins combine with and activate factor VII, this complex then activates factor X. Thus, activated factor X is the reaction where the intrinsic and extrinsic pathways meet, beyond this step is a common pathway. Factor Xa complexes with factor Va in the presence of calcium and phospholipid and converts prothrombin to thrombin. The presence of factor VIIIa and factor Va, catalytic complexes optimally

located on the surface of platelets, allows the rate of thrombin generation to be increased 300000 times. Thus, thrombin and factor Xa act as a positive feedback mechanism for the conversion of prothrombin to thrombin on the platelet surface. (7)

Platelet involvement in thrombus formation is very complex, with adhesion and aggregation resulting from a multitude of reactions. Glycoproteins on the platelet surface bind to exposed adhesive proteins in the vascular subendothelial collagen layer, including von Willebrand factor (vWF), thrombospondin, fibronectin, and vitronectin.2,3 Platelet phospholipase activity is initiated with adhesion, leading to thromboxane A2 production from arachidonic acid, and the platelets secrete active compounds. Adenosine diphosphate, adenosine triphosphate, calcium, and serotonin are released by the dense granules, while the alpha granules release vWF, fibronectin, thrombospondin, vitronectin, platelet-derived growth factor, and b-thromboglobulin. Thromboxane A2 is a potent vasoconstrictor and adenosine diphosphate is a potent aggregating agent in a positive feedback role. Fibrinogen and the other adhesive proteins interact with platelet surface glycoproteins in calcium-dependent reactions to form platelet-platelet bonds. (8)

The vascular endothelium is a heterogeneous, actively functioning unit, through which several homeostatic mechanisms work to prevent thrombus formation. Endothelial cells have high affinity binding sites for thrombin, which can lead to the inactivation of thrombin. Heparan sulfate on the cell surface catalyzes the thrombin-antithrombin III reaction. Prostaglandin generated by the vessel wall causes vasodilation and inhibits platelet aggregation. Normally, platelets may adhere to endothelial cells but do not

necessarily aggregate. Low levels of prostacyclin may lead to platelet aggregation and thrombus formation. (9)

The enzyme responsible for prostacyclin production, prostacyclin synthetase, has a high concentration in the intima and progressively decreases in the external layers of the vessel wall, providing an antithrombogenic environment near the lumen and a more thrombogenic environment deeper in the wall. (10)

2- Stasis

Venous thrombosis often begins in areas of relative or actual stasis as valve cusps and the venous sinuses of the calf muscles. Stasis itself, however, does not cause blood to clot when it is in contact with intact endothelium. Stasis contributes to thrombosis by allowing a localized hypercoagulable state. Static blood does not clear activated coagulation factors, nor does it allow dilution of these activated coagulation factors by nonactivated blood. Additionally, inhibitors of the activated coagulation factors cannot effectively mix with the activated factors in static blood. (11)

Venous stasis can result from immobility, or obstruction to blood flow. Immobility is seen most frequently during surgery and in the early postoperative course, as well as in advanced age and obesity. Extremities immobilized by splints or casts, traction, or paralysis are also associated with venous stasis. The effect of immobility is reflected in higher rates of DVT in patients who have undergone hysterectomy or prostatectomy via the transabdominal route, as opposed to a transvaginal or transurethral procedure(10). Limbs that are paralyzed by stroke have a four to nine times higher incidence of DVT versus no affected limbs, compared with an equal incidence of DVT in the legs of paraplegic individuals. (11)