THROMBOLYTIC THERAPY IN MANAGEMENT OF PERIPHERAL VASCULAR THROMBOSIS

An Essay

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Introduction

Thrombotic complications of diseased vascular tree are the leading cause of morbidity and mortality in most industrialized countries. ***(Eitzman D., et al. 2007)*** Thrombolytic therapy was developed after the pathophysiology of thrombus formation was identified. A variety of agents have been developed, and there is significant debate over which agent offers the best treatment option for a given disorder.***(Bruce Perler., et al. 2005)***

Reperfusion therapy using thrombolytic agents has been shown to be a safe and effective treatment strategy for arterial ischemia, venous thrombosis, massive pulmonary embolism, and acute stroke. Thrombolytic agents have evolved over the course of a few decades, from non fibrin-selective to fibrin-selective agents. The development and modification of these agents have resulted in improved understanding of their pharmacologic attributes, and their effects on the complex molecular events that occur during thrombolysis goal-directed therapies. ***(Kimi L., et al., 2010)***

The streptokinase era dates back to 1933, while ***Tillett***discovered the agent through sheer serendipity, who called it fibrolysin. But first test was carried out on human in 1947 to lyse chronic thoracic empyemas

with considerable success. Due to difficulties in purifying the protein the intravenous administration of streptokinase was delayed. In the 1960s, ***Behringwerke AG and Kabi Pharmacia*** made the drug accessible for prevalent therapeutic use. A significant success came during first trial using streptokinase with acute myocardial infarction, published between 1978 and 1988, compared with conservative treatment or placebo.***(Ramjan Ali., et al., 2014)***

In1980s, there has been an explosions of works in thrombolytic therapy where melanoma tPA were first demonstrate in rabbits with experimental pulmonary embolus in vivo. Tissue plasminogen activator (tPA) originally developed in the mid 1981s by ***Dr B.E. Sobel*** for acute coronary artery occlusion. Recombinant tPA (rtPA) was produced in late 1981s after molecular cloning techniques were used to express human tPA DNA. A predominantly single-chain form of rtPA was eventually accepted in the US for the treatment of acute MI and massive pulmonary embolism.***(Collen D., et al., 2009) , (Wardlaw JM., et al., 2012)***

A recent study provides the evidence to use rtPA in the treatment of acute ischemic stroke. An effort was taken later to lengthen the duration of tPA. Human gene for tPA was modified by genetic engineering where different amino acisd occur at

three locations to yield tencepteplase (TNK-tPA). This modification gives TNK-tPA a longer half life and allowed successful administration as a single bolus in contradiction of the infusion needed for rtPA. TNK-tPA possesses relative resistance to plasminogen inhibitor and more fibrin specific than either tPA. Recent investigation has found that TNK-tPA to be useful in embolic stroke. ***(Collen D., et al., 2009) , (Wardlaw JM., et al., 2012)***

All of the currently approved thrombolytic agents are plasminogen activators (PAs), which induce plasmin action on fibrin contained within a thrombus and, in association with this, produce a greater or lesser degree of plasma fibrinogenolysis (a lytic state). Degradation of fibrin has the beneficial effect of reducing thrombus size (thrombolysis), but at the same time, the PA may cause bleeding by lysis of hemostatic plugs or degradation of the vascular matrix . Re-thrombosis may follow initial reperfusion, generally as a result of a persistent vascular lesion and plasma hypercoagulability. The relationships among these biologic actions of thrombolysis , loss of vascular integrity , re-thrombosis , and the plasma lytic state control the effectiveness and safety of thrombolytic treatment . ***(Vinit B. Amin, et al., 2014)***

Six PAs have been approved by the U.S. Food and Drug Administration (FDA) for use in major

thrombotic diseases: streptokinase (SK), urokinase (UK), alteplase (tissue plasminogen activator [tPA]), anistreplase (anisoylated plasminogen SK [APSAC]), reteplase, and tenecteplase (TNK tPA), although UK is no longer available in the United States and anistreplase is rarely used . Recombinant forms of UK, saruplase (prourokinase [pro-UK], single-chain urokinase-type plasminogen activator [scu-PA]), staphylokinase, and bat-PA (bat plasminogen activator from the salivary gland of Desmodus rotundus); chimerics of tPA and pro-UK, bifunctional agents composed of antifibrin or antiplatelet antibodies (APAs) complexed to PAs; and a recombinant plasminogen that is activated by thrombin are at various stages of testing. ***(Vinit B. Amin, et al., 2014)***

Acute deep vein thrombosis (DVT) is associated with significant morbidity in the form of acute limb-threatening compromise from phlegmasia cerulea dolens, development of the postthrombotic syndrome (PTS), and even death secondary to pulmonary embolism. Initial therapy for DVT is anticoagulation, which inhibits thrombus propagation but lacks the thrombolytic properties to facilitate active thrombus removal. The existing thrombus burden can cause increased venous hypertension from occlusion as well as damage to venous valves by initiating an inflammatory response, which can

ultimately result in PTS in up to half of patients on anticoagulation. The manifestations of PTS include leg pain, swelling, lifestyle-limiting venous claudication, skin hyperpigmentation, venous varicosities, and, in rare cases, venous stasis ulcers. Furthermore, patients with iliocaval DVT and large, free-floating thrombus are at an increased risk for pulmonary embolism despite adequate anticoagulation. .***(Victor J. Marder, et al., 2013)***

Early attempts at thrombus removal with surgical thrombectomy or systemic thrombolysis or both demonstrated reductions in the incidence of PTS but were of limited utility owing to their invasiveness and increased risk of bleeding complications. New minimally invasive endovascular therapies, such as pharmacomechanical catheter-directed thrombolysis, have been proposed, which focus on rapid thrombus removal while decreasing the rate of bleeding complications associated with systemic therapy.***(Victor J. Marder, et al., 2013)***

Intra-arterial thrombolytic treatment is a commonly utilized treatment modality in acute lower limb ischemia. It can offer definitive treatment without the need for major surgery in patients with acute ischemia due to occlusion of a native artery or a bypass graft. Three randomized trials: Rochester, STILE, and TOPAS, which compared intra-arterial catheter-directed thrombolysis to standard surgical