Role of Thrombolytic Therapy in ICU Patients

Essay

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Contents

List of Abbreviations

AMI	:	Acute myocardial infarction
AMI	:	Management of acute MI
APC	:	Activated protein C
APSAC	:	Anisoylated purified streptokinase activator complex
APTT	:	Activated Partial Thromboplastin Time
aPTT	:	Activated partial thromboplastin time
CDT	:	Catheter-directed thrombolysis
CVADs	:	Central venous access devices
DVT	:	Deep vein thrombosis
ED	:	Emergency department
EPCR	:	Endothelial Protein C Receptor
FDA	:	Food and Drug Administration
MRI	:	Magnetic resonance imaging
MW	:	Molecular weight
PAF	:	Platelet-Activating Factor
PCI	:	Percutaneous coronary intervention
PE	:	Pulmonary embolism
PT	:	Prothrombin time
RV	:	Right ventricular
SK	:	Natural streptokinase
STEMI	:	ST-elevation myocardial infarction
TF	:	Tissue Factor

List of Abbreviations (Cont.)

TFPI	:	Tissue Factor Pathway Inhibitor
TM	:	T-thrombomodulin
TSR	:	Thrombin-sensitive region
TXA2	:	Thromboxane A2
uPA	:	Urinary-type plasminogen activator
US	:	Ultrasound
VAE	:	Venous Air Embolism

List of Tables

List of figures

Introduction

Thrombosis is an important part of the normal hemostatic response that limits hemorrhage caused by microscopic or macroscopic vascular injury. Physiologic thrombosis is counterbalanced by intrinsic antithrombotic properties and fibrinolysis. Under normal conditions, a thrombus is confined to the immediate area of injury and does not obstruct flow to critical areas, unless the blood vessel lumen is already diminished, as it is in atherosclerosis **(Hoehn et al., 2010).** Under pathological conditions, a thrombus can propagate into otherwise normal vessels. A thrombus that has propagated where it is not needed can obstruct flow in critical vessels; it can also obliterate valves and other structures that are essential to normal hemodynamic function **(Hoehn et al., 2010).**

The thrombolytic agents available today are serine proteases that work by converting plasminogen to the natural fibrinolytic agent plasmin. Plasmin lyses clot by breaking down the fibrinogen and fibrin contained in a clot **(Sikri and Bardia, 2007).**

The thrombolytic drugs include: Reteplase (Retavase), Streptokinase (Kabikinase, Streptase), Urokinase (Abbokinase) and other types. These drugs are most effective if administered immediately after it has been determined they are clinically appropriate. The advantage of administration is highest within the first sixty minutes after a thrombotic event, but may extend up to six hours after the start of symptoms (**Cindy et al., 2003).**

Indication of thrombolytic therapy: Acute myocardial infarction (AMI), Deep vein thrombosis (DVT), Pulmonary embolism (PE), Acute ischemic stroke (AIS), Acute

peripheral arterial occlusion and Occlusion of indwelling catheters (**Ouriel, 2004).**

Generally, thrombolytics will not be given if you have: a recent head injury, Bleeding problems, Bleeding ulcers, Pregnancy, Surgery, taken blood thinning medications such as coumadin, trauma and uncontrolled high blood pressure (**Clin Geriatr, 2006).**

Complications of thrombolytic therapy include hemorrhage, allergic reactions, embolism, stroke, and reperfusion arrhythmias, among others. The most feared complication of fibrinolysis is intracranial hemorrhage (ICH), but serious hemorrhagic complications can occur from bleeding at any site in the body (**Hoffman et al., 2008)** . Overdoses of fibrinolytic agents can cause severe hemorrhagic complications. Overdose most often occurs when a full dose of a fibrinolytic agent is given to a small patient with a low body weight **(Hoffman et al., 2008)**.

Physiology of Haemostasis And Fibrinolytic System

Hemostasis is a dynamic process resulting from the balance between procoagulant and anticoagulant factors **(Hoehn et al., 2010).**

Three intertwind processes ensure that blood remains in aliquid state until vascular injury occurs: primary hemostasis, secondary hemostasis, and fibrinolysis (**Hoehn et al., 2010).**

Physiology of primary hemostasis:

Haemostasis is achieved by different mechsnisms including:

Vascular spasm:

Vascular spasm is the blood vessels' first response to injury. The damaged vessels will constrict which reduces the amount of blood flow through the area and limits the amount of blood loss. This response is triggered by factors such as a direct injury to vascular smooth muscle, chemicals released by endothelial cells and platelets, and reflexes initiated by local pain receptors .The spasm response becomes more effective as the amount of damage is increased. Vascular spasm is much more effective in smaller blood vessels **(Hoehn et al., 2010)**.

Formation of platelet plug:

- When the endothelium is damaged, the normally isolated, underlying collagen is exposed to circulating platelets, which bind directly to collagen with collagen-specific glycoprotein Ia/IIa surface receptors. This adhesion is strengthened further by von Willebrand factor (vWF), which is released from the endothelium and from platelets; vWF forms additional links between the

platelets' glycoprotein Ib/IX/V and the collagen fibrils. These adhesions also activate the platelet **(Clemetson, 2012).**

- Activated platelets release the contents of stored granules into the blood plasma. The granules include ADP, serotonin, platelet-activating factor (PAF), vWF, platelet factor 4, and thromboxane A2 (TXA2), which, in turn, activate additional platelets. The granules' contents activate a Gq-linked protein receptor cascade, resulting in increased calcium concentration in the platelets' cytosol. The calcium activates protein kinase C, which, in turn, activates phospholipase A2 (PLA2). PLA2 then modifies the integrin membrane glycoprotein IIb/IIIa, increasing its affinity to bind fibrinogen. The activated platelets change shape from spherical to stellate, and the fibrinogen cross-links with glycoprotein IIb/IIIa aid in aggregation of adjacent platelets **(Clemetson, 2012).**

Physiology of secondary hemostasis

- The coagulation cascade of secondary hemostasis has two pathways which lead to fibrin formation. These are the contact activation pathway (also known as the intrinsic pathway), and the tissue factor pathway (also known as the extrinsic pathway). It was previously thought that the coagulation cascade consisted of two pathways of equal importance joined to a common pathway. It is now known that the primary pathway for the initiation of blood coagulation is the tissue factor pathway. The pathways are a series of reactions, in which a zymogen (inactive enzyme precursor) of a serine protease and its glycoprotein co-factor are activated to become active components that then catalyze the next reaction in the cascade, ultimately resulting in cross-linked fibrin **(Clemetson, 2012).**

Tissue factor pathway (extrinsic):

The main role of the tissue factor pathway is to generate a "thrombin burst, " a process by which thrombin is released very rapidly. FVIIa circulates in a higher amount than any other activated coagulation factor:

- Following damage to the blood vessel, FVII leaves the circulation and comes into contact with tissue factor (TF) forming an activated complex (TF-FVIIa).
- TF-FVIIa activates FIX and FX.
- FVII is itself activated by thrombin, FXIa, FXII and FXa.
- The activation of FX (to form FXa) by TF-FVIIa is almost immediately inhibited by tissue factor pathway inhibitor (TFPI).
- FXa and its co-factor FVa form the prothrombinase complex, which activates prothrombin to thrombin.
- Thrombin then activates other components of the coagulation cascade, including FV and FVIII (which activates FXI, which, in turn, activates FIX), and activates and releases FVIII from being bound to vWF.
- FVIIIa is the co-factor of FIXa, and together they form the "tenase" complex, which activates FX; and so the cycle continues ("Tenase" is a contraction of "ten" and the suffix "-ase" used for enzymes) (**Clemetson, 2012).**

Contact activation pathway (intrinsic):

The contact activation pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor

XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa **(Clemetson, 2012).**

Final common pathway:

Thrombin has a large array of functions. Its primary role is the conversion of fibrinogen to fibrin, the building block of a hemostatic plug. In addition, it activates Factors VIII and V and their inhibitor proteinC (in the presence of thrombomodulin), and it activates Factor XIII, which forms covalent bonds that crosslink the fibrin polymers that form from activated monomers **(Clemetson, 2012)**.

Following activation by the contact factor or tissue factor pathways, the coagulation cascade is maintained in a prothrombotic state by the continued activation of FVIII and FIX to form the tenase complex, until it is down-regulated by the anticoagulant pathways **(Clemetson, 2012)**

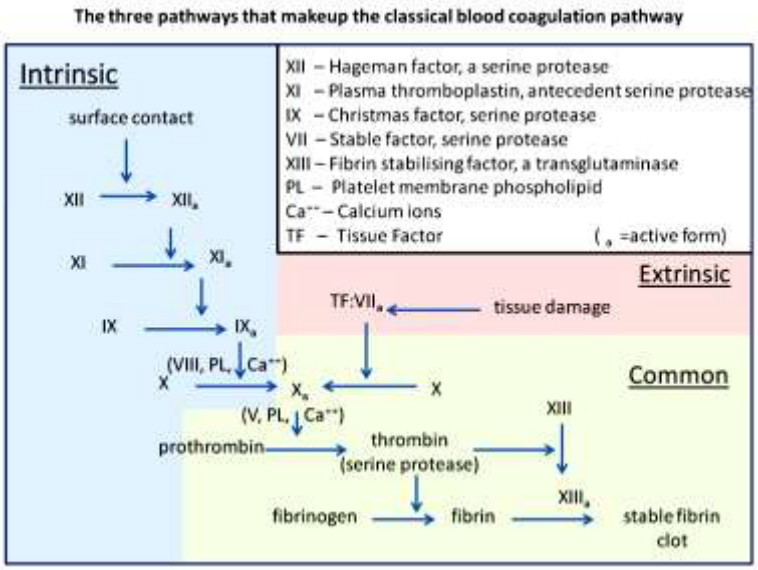

Fig. (1): The three pathways that makup the classical blood coagulation pathway **(Clemetson, 2012)**.

Fibrinolytic system:

Fibrinolytic system is a highly regulated mechanism that, on deposition of fibrin within the vascular system, converts the proenzyme plasminogen into the active enzyme plasmin, which in turn degrades fibrin (Fig. 2) (**Caldwell et al., 2006)**.

Under normal conditions, plasminogen-to-plasmin conversion is regulated by such activators as tissue Plasminogen Activator (t-PA), urokinase plasminogen activator, and activated factor XII. These activators (profibrinolytic drivers) are opposed by such antiactivators as t-PA inhibitors [mainly, Plasminogen Activator Inhibitor (PAI)], plasmin inhibitor, and Thrombin-Activatable Fibrinolysis Inhibitor (TAFI), which cumulatively act as antifibrinolytic drivers. Any perturbation of this balance may result in hyperfibrinolysis, which increases the risk of hemorrhage, or hypofibrinolysis, which increases the risk of thrombosis. Plasma hyperfibrinolysis has been reported in patients with liver cirrhosis, but its mechanistic role in bleeding is still debated **(Caldwell et al., 2006)**.

Cirrhosis has been variably associated with laboratory changes favoring hyperfibrinolysis, such as increased levels of t-PA and reduced levels of plasmin inhibitor and TAFI, but also with changes favoring hypofibrinolysis, such as reduced levels of plasminogen and increased levels of PAI. Hence, although contrasting results have been reported, the balance of fibrinolysis is probably restored in patients with liver cirrhosis by the parallel changes in profibrinolytic and antifibrinolytic drivers **(Colucci et al., 2003)**.

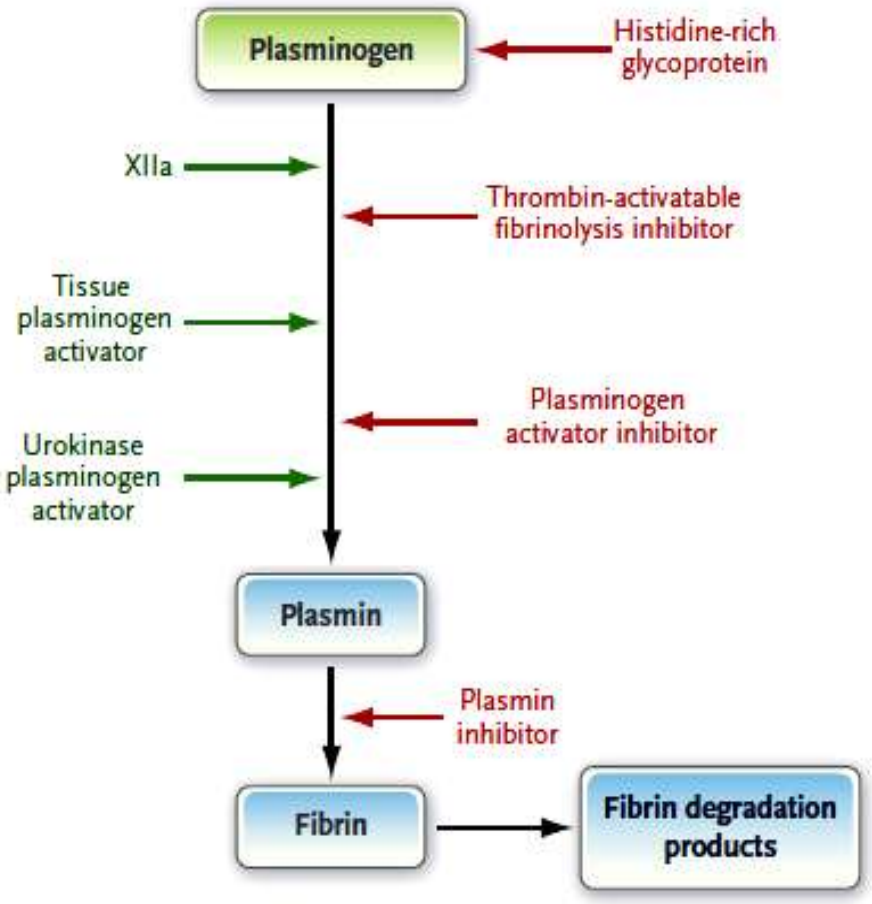

Fig. (2): Fibrinolysis activation and inhibition. Green and red arrows represent activators and antiactivators, respectively. XIIa denotes activated factor XII (**Caldwell et al., 2006).**

New aspect of coagulation cascade.

Several coagulation cascade models have been proposed, including the intrinsic and extrinsic pathway model and the more recent cell-based mode

The cell-based model better explains the mechanism of hemostasis in vivo and includes the important interactions between cells directly involved in hemostasis. (i.e. tissue