Outcome in Thromboprophylaxis in I.C.U. Patients

Comparative Study Between Heparin and the New Generation Antithrombotic Agent (Fragmin)

Thesis Submitted for Partial Fulfillment of the M.D. Degree in Anesthesia

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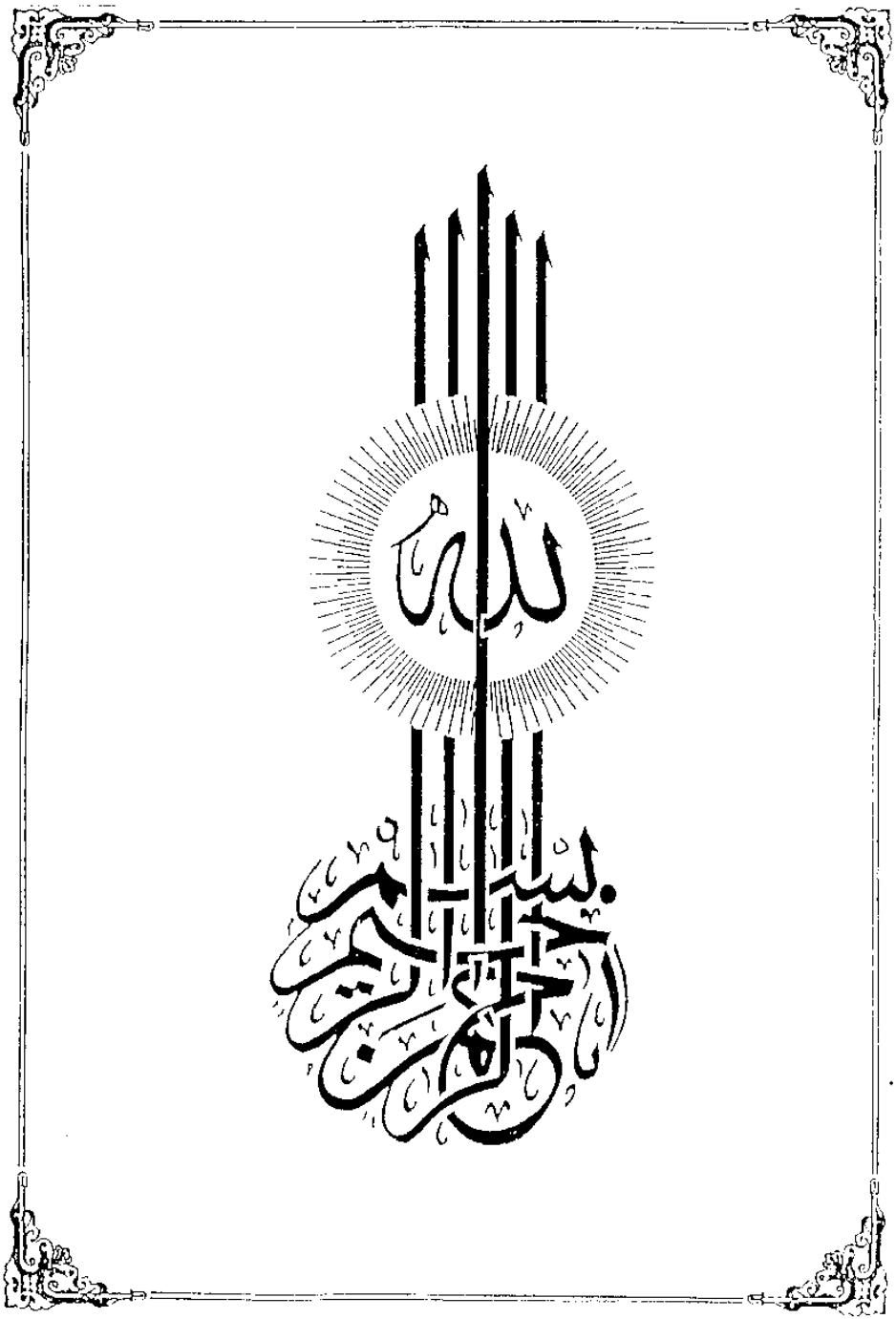

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The in vivo action of the clotting mechanism is balanced by limiting reactions that normally prevent clots from developing in uninjured vessels and maintain the blood in a fluid state. It is worth emphasizing that a balance between many complex, interrelated systems must be maintained to prevent hemorrhage while preventing intravascular coagulation.

The factors involved include the endothelium of the blood vessels and the collagen underlying it, vascular tone, the platelets, the clotting and fibrinolytic systems, and the flow characteristics of blood within the blood vessels ***(Clouse and Comp, 1986)***.

Physiology of Blood Coagulation :

(1) Role of platelets.

(2) Clotting mechanism (intrinsic and extrinsic).

(3) Endogenous inhibition of coagulation.

(4) Fibrinolysis.

[1] Platelets :

Platelets have multiple and over-expanding roles in hemostasis. They are complex cytoplasmic fragments released from bone marrow megakaryocytes under the control of thrombopoietin. The platelets contain granules, a lipid membrane, microtubules, and a canalicular system. Each participates in the process of coagulation ***(Glenn, 1992)***.

[2] The Clotting Mechanism :

The clotting mechanism responsible for the formation of fibrin involves a cascade of reactions in which inactive enzymes are activated and the activated enzymes in turn activate other inactive enzymes ***(Furie and Furie, 1992)***.

The fundamental reaction in the clotting of blood is conversion of soluble plasma protein fibrinogen to insoluble fibrin **(figure 3)**.

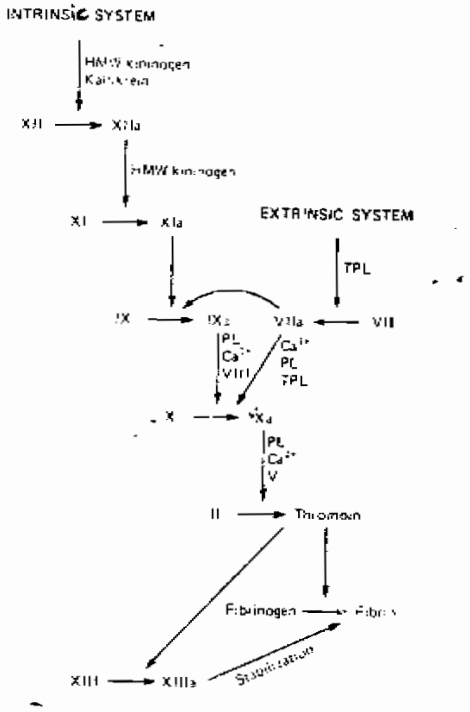

Figure (3) : The clotting mechanism. a, active form of clotting factor; HMW, high-molecular-weight; PL, platelet phospholipid; TPL, tissue thromboplastin (*Ganong, 1993*).

The process involves the release of 2 pairs of polypeptides from each fibrinogen molecule. The remaining portion, fibrin monomer, then polymerizes with other monomer molecules to form fibrin. The fibrin is initially a loose mesh of interlacing strands.

It is converted by the formation of covalent cross-linkages to a dense, tight aggregate. This latter reaction is catalyzed by factor III, the fibrin-stabilizing factor, and requires Ca^{++}.

The conversion of fibrinogen to fibrin is catalyzed by thrombin. Thrombin is a serine protease that is formed from its circulating precursor, prothrombin, by the action of activated factor X.

Factor X can be activated by reactions in either of 2 systems, an intrinsic and an extrinsic system **(figure 3)** ***(Ganong, 1993)***.

Most of the activated factors in the coagulation pathways are serine protease enzymes, two exceptions being factor V and factor VIII (antihemophilic factor which are enzyme cofactors ***(Gordon-Smith, 1995)***.

All the factors necessary for coagulation are present in the undisturbed circulation in an inactive form.

The initial reaction in the intrinsic system is conversion of inactive factor XII to active factor XII (XIIa). This activation is catalyzed by high molecular weight kininogen and kallikrein. Activation in vivo occurs when blood is exposed to collagen fibers underlying the endothelium in the blood vessels. Active factor XII then activates factor XI and active factor XI activates factor IX. Activated factor IX forms a complex with factor VIII, activating factor X. Phospholipids from aggregated platelets (PL) and Ca^{++} are necessary for full activation of factor X.

The extrinsic system is triggered by the release of tissue thromboplastin, a protein-phospholipid mixture that activates factor VII. The tissue thromboplastin and factor VII activate factors IX and X in the presence of PL, Ca^{++} and factor V. Activated factor X catalyses the conversion of prothrombin to thrombin ***(Ganong, 1993)***.

These terms (intrinsic and extrinsic) only have meaning in relation to the coagulation screening tests, the activated partial thromboplastin time (APTT) also known as partial thromboplastin time with kaolin (PTTK) for the intrinsic system and the prothrombin time (PT) for the extrinsic system ***(Rapaport, 1983)***.

Except for the first two steps in the intrinsic pathway, calcium ions are required for promotion of all the reactions. Therefore, in the absence of calcium ions, blood clotting will not occur. Fortunately, in the living body, the calcium ion concentration rarely falls low enough to affect significantly the kinetics of blood clotting. The reason for this is that before calcium ions concentration can fall that low, the diminished level of calcium ions will likely kill the person by causing muscle tetany throughout the body, especially of the respiratory muscle ***(Guyton, 1986)***.

Most of the coagulation proteins are synthesized by the liver. Their normal structure and function are dependent upon normal hepatic activity. Four of the clotting factors (II, VII, IX, X) are vitamin K dependent factors, because they require vitamin K for their proper synthesis in the liver. After these factors have been synthesized, they undergo a final enzymatic reaction which requires the presence of vitamin K. A carboxyl moiety is added to each factor and enables the vitamin K dependent factors to bind via calcium to phospholipid surfaces. Without vitamin K, these proteins are produced in normal amounts by the liver, but are not functional because they cannot bind to phospholipid surfaces. The coumadin-

like drugs compete with vitamin K for binding sites on the hepatocyte and in this way coumadin inhibits carboxylation of the vitamin K dependent factors.

Of the four vitamin K dependent factors, factor VII has the shortest half-life. It is the first clotting factor to disappear from the circulation when the patient is placed on coumadin.

Only one factor, coagulant factor VIII is thought to have some extrahepatic origin. Factor VIII circulates as a huge plasma protein and is really a complex of two components, each under separate genetic control. The high molecular weight portion (VIII R:Ag) contains both the factor VIII antigen and the von Willebrand factor (vWF).

The vWF has two major functions, it mediates adhesion of platelets to collagen in the subendothelial layers of blood vessels after they have been injured during the process of primary hemostasis and it serves as a carrier protein for the smaller moiety of the factor VIII molecule. This smaller moiety contains the factor VIII coagulant activity (VIIIc).

Absence of the smaller portion of the factor VIII molecule (VIIIc), leads to hemophilia A.

Because the vWF also serves as a carrier protein for the coagulant factor VIII portion, deficiencies of vWF make the patient appears to have both a defect in primary hemostasis and hemophilia A. Restoration of vWF levels returns the level of coagulant factor VIII to normal ***(Petrovitch, 1996)***.

[3] Endogenous Inhibition of Coagulation :

The tendency of blood to clot is balanced in vivo by limiting reactions that tend to prevent clotting inside the blood vessels and to break down any clots that do form.

These reactions include :

- Removal of some activated clotting factors from the circulation by the liver and the reticuloendothelial system and reduction in the supply of clotting factors to the degree that they are used up during clotting.

- Another reaction is the interaction between the platelet-aggregating effect of thromboxane A_2 and the anti-aggregating effect of prostacyclin which causes clots to form at the site when a blood vessel is injured but keeps the vessel lumen free of clot.

- Antithrombin III is a circulating protease inhibitor synthesized by the endothelial cells in the liver. It has a molecular weight of 58,000 daltons ***(Fair and Bahnak, 1984)***. It binds to the serine protease in the coagulation system, blocking their activity as clotting factors. This binding is facilitated by heparin, a naturally occurring anticoagulant that is a mixture of sulfated polysaccharides with molecular weights averaging 15,000 - 18,000. The clotting factors that are inhibited are the active forms of factors IX, X, XI, XII. The luminal surface of the endothelial layer expresses a heparin sulfate substance much like heparin. This heparin sulfate has the ability to weakly stimulate antithrombin III. Endogenous heparin is also synthesized by mast cells. The endothelial location of heparin sulfate permits binding and activation of ATIII at the blood-surface interface where activated factors of the coagulation cascade are being generated ***(Petrovitch, 1996)***.

- The endothelium of the blood vessels also plays an active role in preventing the extension of clots to normal blood vessels. All endothelial cells except those in the cerebral microcirculation produce thrombo-modulin, a thrombin-binding protein that converts thrombin into protein C activator. This activates protein C **(figure 4)**, a naturally occurring anticoagulant protein that inactivates factors V and VIII and inactivates an inhibitor of tissue plasminogen activator, increasing the formation of plasmin ***(Ganong, 1993)***.

The action of activated protein C is aided by a cofactor named protein S. Both protein C and protein S are vitamin K dependent proteins ***(Petrovitch, 1996)***.

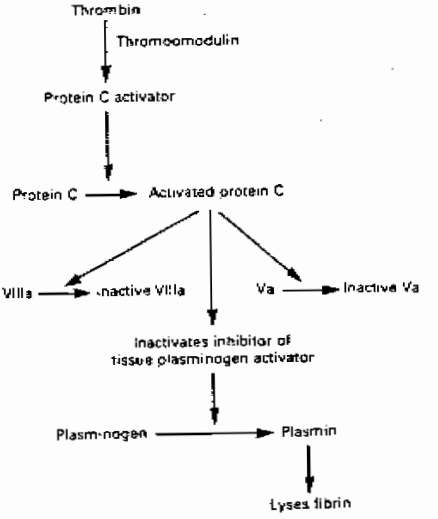

Figure (4) : The fibrinolytic system and its regulation by protein C ***(Wessler and Gitel, 1984)***.

[4] Fibrinolysis :

The process of fibrinolysis involves the conversion of plasminogen to plasmin, the active fibrinolytic enzyme. Plasmin does not circulate in the blood freely because it would rapidly be attached by antiplasmins present in the blood stream. Instead, the precursor to plasmin, plasminogen, circulates in the blood stream. When plasminogen comes into contact with fibrin, plasminogen preferentially binds to the fibrin clot. Bound to fibrin, plasminogen is converted to plasmin by tissue plasminogen activator (t-PA). The plasmin formed has a specific binding site for fibrin. This same binding site is also involved in the interaction of plasmin with the plasmin inhibitor, alpha2-antiplasmin.

As long as plasmin remains bound to fibrin, even though actively involved in degrading the fibrin clot, alpha2-antiplasmin cannot neutralize the enzyme. However, as soon as the binding site is free when plasmin is released into the blood stream, alpha2-antiplasmin will rapidly neutralize the plasmin. These antiplasmins, which circulate in blood, prevent wide spread fibrinolysis.

Only plasmin bound to fibrin is shielded from antiplasmin attack. Fibrinolysis is also limited to the site of fibrin formation because t-PA only activates plasminogen which is bound to fibrin ***(Petrovitch, 1996)***.

Human t-PA is now produced by recombinant DNA techniques and is available for clinical use. It lyses clots in the coronary arteries if given to patients soon after the onset of myocardial infarction. Streptokinase, a bacterial enzyme, and urokinase, an enzyme produced by kidney cells, are also fibrinolytic and are used in the treatment of early myocardial infarction ***(Furster, 1992)***.

The primary action of plasmin is to degrade fibrin clots. The degradation products produced are called fibrin degradation products (FDPs) or fibrin split products (FSPs). Their structure varies according to whether plasmin cleaves fibrinogen, fibrin that is cross-linked, or fibrin that is not cross-linked, etc. Under normal circumstances, FDPs are removed from the blood by the liver, kidney, and reticuloendothelial system and have half-lives of about nine hours. If the FDPs are produced at a rate that exceeds their normal clearance, they will accumulate. In high concentrations, FDPs act as anticoagulants. The FDPs impair platelet function, inhibit thrombin, and prevent the cross-linking of fibrin strands. In such high concentrations, the FDPs lead to bleeding which is not due to a coagulation defect, but rather due to the accumulation of FDPs which act as *inhibitors* to coagulation ***(Petrovitch, 1996)***.