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STUDY OF THE PROPHYLACTIC ADMINISTRATION OF EITHER FRESH BLOOD, FRESH FROZEN PLASMA AND PLATELETS OR TRANEXAMIC ACID ON HAEMOSTASIS AFTER CARDIOPULMONARY BYPASS

Thesis

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By

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INTRODUCTION

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PHYSIOLOGY OF HAEMOSTASIS

Haemostasis was formerly defined as the process by which bleeding from an injured blood vessel is arrested.[1] However, it has been recently described to have several important functions:

1. To maintain blood in a fluid state whilst it remains circulating within the vascular system.
2. To arrest bleeding at the site of injury or blood loss by formation of haemostatic plug.
3. To ensure the eventual removal of the plug when healing is completed.[2]

There are at least five different components involved in haemostasis; blood vessels, platelets, plasma coagulation factors, their inhibitors & the fibrinolytic system.[2]

I. BLOOD VESSELS:

- **General structure of the blood vessel:**

The blood vessel wall has three layers: intima, media & adventitia. The intima consists of endothelium and subendothelial connective tissue. Endothelial cells form a continuous monolayer lining all blood vessels. They have three important characteristics:

First, they are non thrombogenic, i.e. they promote maintenance of blood in its fluid state; second, they play an active role in supplying nutrients to the subendothelial structures, and third, they act as a barrier to macromolecules and particulate matter circulating in the blood stream.[2]

- **Endothelial cell function:**

The luminal surface of the endothelial cell contains heparan sulfate and other glycosaminoglycans, which are capable of activating antithrombin (AT), an important inhibitor of coagulation enzymes.

Also, the endothelium produces von Willebrand Factor (vWF) essential for platelet adhesion to the subendothelium. This is stored in specific granules called Weibel Palade bodies and is secreted partly into the circulation and partly towards the subendothelium. vWF plays an important role in promoting platelet adhesion.

The endothelial cell participates in vasoregulation by producing and metabolizing numerous vasoactive substances. On one hand, it metabolizes and inactivates vasoactive peptides such as bradykinin; on the other hand, it can also generate angiotensin II, a local vasoconstrictor, from circulating angiotensin I. Under appropriate stimulation, the endothelial cell can produce vasodilators such as nitric oxide (NO) and prostacyclin or vasoconstrictors such as endothelin and thromboxane.

The subendothelium consists of connective tissues composed of collagen, elastic tissues, proteoglycans and non collagenous glycoproteins, including fibronectin and vWF. After vessel wall damage has occurred, these components are exposed and are then responsible for platelet adherence. This appears to be mediated by vWF binding to collagen, particularly under high shear rate.

- **Vasoconstriction:**

Vessels with muscular coats contract following injury thus helping to arrest blood loss. Although not all coagulation reactions are enhanced by reduced flow, this probably assists in the formation of a stable fibrin

plug. Vasoconstriction also occurs in the microcirculation in vessels without smooth muscle cells. Endothelial cells themselves can produce vasoconstrictors such as angiotensin II. In addition, activated platelets produce thromboxane A_2 (TXA_2) which is a potent vasoconstrictor.[2]

II. PLATELETS:

- **Platelet structure:**

Platelets are small fragments of cytoplasm derived from megakaryocytes. They do not contain a nucleus and are bounded by a typical lipid bilayer membrane. This membrane is the site of interaction with the plasma environment and with damaged vessel wall. It consists of phospholipids, cholesterol, glycolipids and at least nine glycoproteins, named GpI- GpIX. The membrane also expresses specific receptors for several coagulation proteins such as factor IX and factor VIII.[2]

- **Platelet function in the haemostatic process:**

The main steps in platelet functions are adhesion, activation with shape change, and aggregation as shown in Figure 1.

When the vessel wall is damaged, the subendothelial structures are exposed. Surface-bound vWF binds to GpIb on circulating platelets resulting in an initial monolayer of adhering platelets. Binding via GpIb activates platelets resulting in immediate shape change from a disc to a tiny sphere with numerous pseudopods. After adhesion, platelets stick to one another to form aggregates. Fibrinogen, fibronectin and the glycoprotein Ib-IX and IIbIIIa complexes are essential at this stage to increase the cell to cell contact and facilitate aggregation. Also, the release of adenosine diphosphate (ADP) and TXA2 from injured vessels lead to release of platelet granules and secondary platelet aggregation.[2]

Platelet Functions

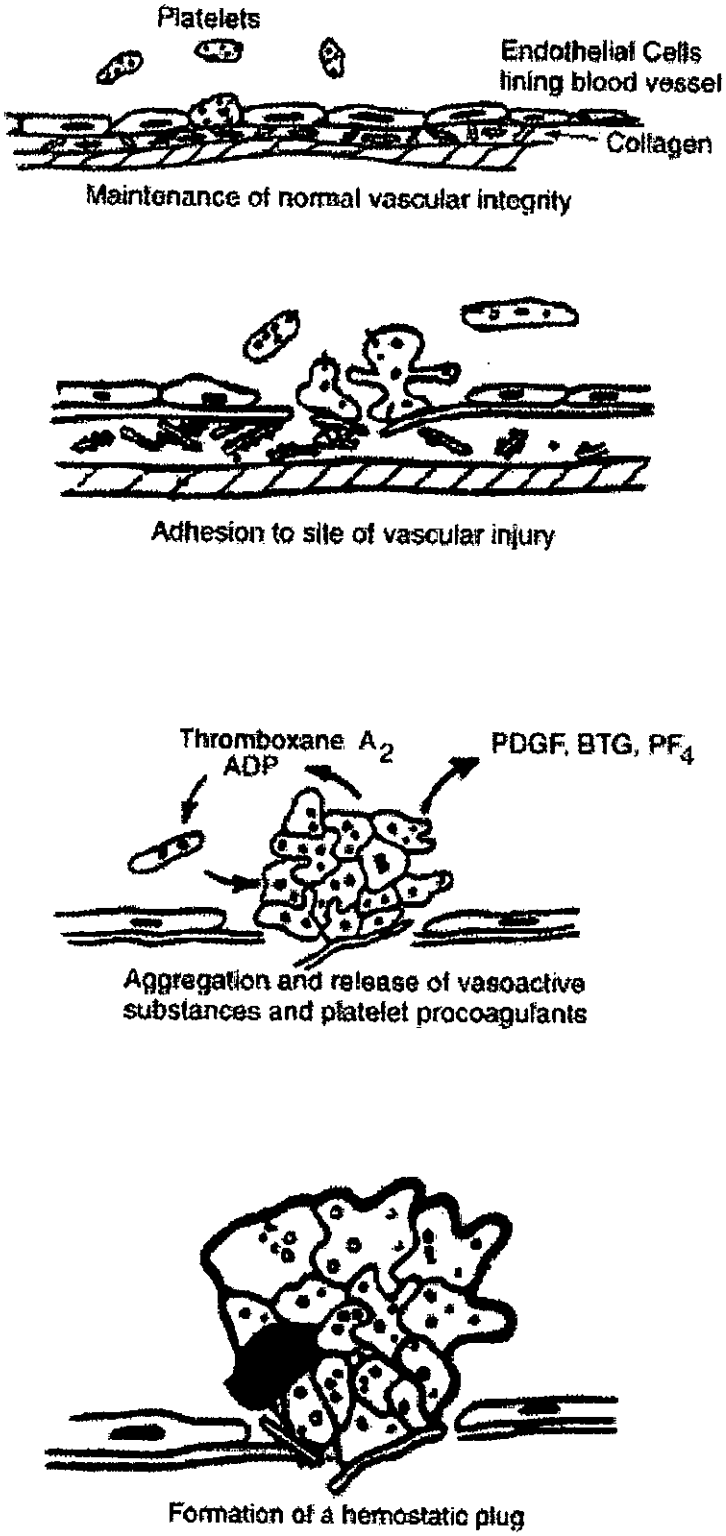

Figure (1): The response of the blood vessels and platelets to injury (After Dacie & Lewis Practical Haematology 9th ed).[2]

III. BLOOD COAGULATION:

The coagulation factors circulate in the plasma as cofactors or as procoagulants, and when activated supply some of the components needed for clot formation. According to the international nomenclature system, coagulation cofactors and procoagulants were assigned roman numerals in the order of their discovery and do not correspond to their location in the coagulation sequence of activation.

The coagulation factors are generated in the liver cells, except for Factor VIII (at least the von Willebrand's portion), which is produced in multiple organs, possibly the endothelial cells and megakarocytes (Table 1).

The model generally used to describe the mechanism of coagulation is the cascade system. The cascade is separated into three areas: the intrinsic system, the extrinsic system, which is activated by vascular injury, and, the common pathway, which is set into motion by activation from the intrinsic and/or the extrinsic pathway.

The coagulation factors, except for calcium and thromboplastin, are proteins and are involved in a sequential reaction or coagulation cascade. The last step of the cascade leads to insoluble fibrin as an end product.

The extrinsic pathway is initiated by the release of tissue thromboplastin (Factor III) which is exposed to the blood when there is damage to the blood vessel. Factor VII, which is a circulating coagulation factor, forms a complex with tissue thromboplastin and calcium. This complex rapidly converts Factor X to the enzyme form Factor X_a. Factor X_a catalyzes the prothrombin (Factor II) to thrombin (Factor II_a) reaction that is needed to convert fibrinogen (Factor I) to fibrin.

The intrinsic pathway of Coagulation is activated when circulating Factor XII comes in contact with and is bound to a negatively charged surface. This causes a change in the molecular configuration of Factor XII and in concert with High Molecular Weight Kininogen (HMWK) and prekallikrein it becomes an active enzyme, XII_a. This activated enzyme is then able to bring about a similar change in Factor XI. After activation, Factor XI_a, in a calcium dependent reaction, converts Factor IX to its active form, Factor IX_a. A phospholipid surface is also needed for Factor IX_a conversion and is provided by activated platelets, as Platelet Factor Three (PF3). Factor IX can also be activated by the tissue factor, Factor VII complex; the initiating complex of the extrinsic pathway. Factor X can be activated to Factor X_a by either the Factor VII_a complex or by the complex of Factor IX_a and Factor VIII. Factor $\mathbf{X_a}$ in the presence of Factor V, calcium and phospholipid surface converts Factor II (prothrombin) to Factor II_a (thrombin) which converts Factor I (fibrinogen) to fibrin (Figure 2).[3]