Comparative Study Between Different Types of Priming Solution of Extracorporeal Circulation on Coagulation Profile In Open Heart Surgery

Thesis

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ACT .....Activated clotting time
ADP .....Adenosine diphosphate
APTT .....Activated partial thromboplastin time
AT III.....Antithrombin III
ATP.....Adenosine triphosphate
BT .....Bleeding time
B-TG.....B-thromboglobulin
CPB.....Cardiopulmonry bypass
ECC .....Extracorporeal circulation]
FDP.....Fibrin degradation product
GP .....Glycoprotein
Hb .....Hemoglobin
HES.....Hydroxyethyl storch
HMW .....High molecular weight
ICU .....Intensive care unit
PAIS .....Plasminogen-activator inhibitors
PGI_2 .....Prostaglandin I_2
PT.....Prothrombin time
TPA.....Tissue plasminogen activator
TT .....Thrombin time
Tx A_2 .....Thromboxane A_2
VWF .....Von Willebrand factor
X_a ..... Activated factor X

Introduction

The technique of Cardiopulmonary Bypass (CPB) is a common procedure in cardiac surgery. Although (CPB) is considered safe, it disturbs the hemostatic system, which may cause severe bleeding complications, thrombocytopenia, and/ or platelets dysfunction ***(Menichetti et al., ١٩٩٦).***

These complication are though to be due to exposure to artificial surface of pump circuit, surgical traumas, hemodilution, intra-operative high dose of heparin, depth of hypothermia ***(Condo et al., ١٩٩٤).***

In addition to passive dilutional effect, prime composition also impact hemostasis either Ringer`s solution or High molecular weight hydroxyethyl starch or Albumin ***(Kuitunen et al., ١٩٩٣).***

The solution used to prime the CPB varies widely, there is still no consensus in the ideal priming solution, particulary with regard to hemostasis ***(Tobias, ١٩٩٦).***

During CPB, blood is continuously exposed to the nonendothelial, synthetic surface of the extracorporeal oxygenation circuit ***(Westaby, ١٩٩٧).***

Platelts adhustion and protein denaturation are possible sequelae of this blood/surface contact. Denaturated protein result in cellular aggregation, sledging and microthrombosis. Denaturation of red cell membrane induces a release of

adenosine diphosphate (ADP), which leads to aggregation. The viscious cycle is continued as aggregated platelets release more ADP, promoting further platelets aggregation ***(Born et al., ١٩٩٦).***

Preexpose of synthetic surface to Albumin (coating) decrease the affinity of platelets to synthetic surface ***(Campbel, and Addonizio, ١٩٨٨)***. Platelets granule release would be reduced and morphologic integrity of platelets would be preserved when using surface absorbed Albumin ***(Addonizio et al., ١٩٩٩).***

Impairment in platelets function secondary to CPB is one of the most important reasons for enhanced and prolonged bleeding in open heart surgery ***(Addonizio et al., ١٩٩٩).***

Approximately ١٠% - ٢٠% of patients undergoing cardiac surgery procedures exhibit inadequate hemostasis varying in its duration and severity. This patient often require treatment with hemologous blood or blood products ***(Ellison and Jones, ١٩٩٩)***. Surgical reexploration is required in approximately ٣% of these patient ***(Harker, ١٩٩٦).***

Hydroxyethyl starch (HES-heastril) has been showen to be an effective expender of the intravascular volume ***(Halonen et al., ١٩٨٧)***. However like other artifical colloids, HES may have adverse effect on hemostasis ***(Strauss et al., ١٩٩٨)***. Heastril may affect the hemostasis mechanism by depressing platelets function, by lowering plasma levels of clotting factors via haemodilutional or via other mechanism and finally, by increase

fibrinolysis. These effect of HES often result in varying degrees of subclinical coagulopathy ***(Stump et al., ١٩٨٥).***

The ideal choice of priming solution of CPB and its influences on the hemostasis system are not clear. Addition of Albumin was reported to inhibit platelets damaging by blood surface interactions(coating) ***(Kirklin et al., ١٩٨٧).***

Aim of the Work:

The aim of these study is to compare the effect of different types of priming solution of CPB including Ringer`s, Haestril, Albumin on coagulation profile.

Physiology of Coagulation and Hemostasis in Adults and Pediatrics

The hemostatic system serves to minimize blood loss from the vascular space and maintains the blood as a cellular and protein suspension to flow to peripheral tissues. Normal hemostasis is dependent on the interactions of the components of blood vessel walls with the circulating cellular elements and proteins. Cardiac surgery would not be possible without some control of the hemostatic system to prevent thrombosis during cardiopulmonary bypass (CPB) and to decrease post-operative blood loss ***(Spiess andChang, ١٩٩٣).***

The hemostatic system is divided into ٣ subdivisions i.e. vascular system, platelets and blood coagulation system. Synopsis of hemostasis is illustrated in Fig. (١).

The Vascular System:

The vessel wall is a metabolically and physically active organ system, which affects the hemodynamic function, thrombosis and hemostasis. In the resting state, blood is actively maintained in a liquid form by endothelial cells and circulating plasma protein inhibitors, when the vascular integrity is disrupted or the endothelium becomes inflamed coagulation is initiated. Vasoconstriction is the immediate local response of the vascular system to a break in integrity. The

vascular smooth muscle cells are responsible for maintenance of vascular tone and synthesis of elastin, collagen and glycosaminoglycan ***(Boyle et al., ١٩٩٧).*** Endothelial cells synthetize enzymes, coagulation factors, proteins and prostaglandins e.g. PGI_2, thrombomodulin, heparin like substances and plasminogen activators, which, act to prevent thrombosis. It also synthetize fibronectin, Von Willebrand factor, lipoprotein lipase, plasminogen activator inhibitors and endothelin (a protein vasoconstrictor peptide). The eicosanoids prostacyclin and thromboxane as produced by endothelial cells influence the interaction between platelets and vessels wall ***(Havel et al., ١٩٩٢).***

Fig. (١): Hemostasis: a synopsis. The sequential events comprising the process of hemostasis are shown in the center following the central solid arrows. At each step activators (dotted arrows on the left) and inhibitors (dashed arrows on the right) interact to provide a finely

controlled process. VWF. Von Willebrand factor; PGIs, prostaglandin Is; ADP, adenosine diphosphate ***(Colman et al., ١٩٨٧).***

Platelets:

The primary process of hemostatic phases after immediate vasospasm is the formation of hemostatic plug. This is achieved by platelet adhesion, aggregation, and release of granules and other products. This initiation of the hemostatic process is followed by the activation of the clotting process to produce fibrin ***(O'Reilly, ١٩٩٨).***

The first step in this process is the interaction between platelets and thrombogenic surface, so platelets adhere to the collagen of the damaged endothelial cells or subendothelial layer specifically to fibrinoactin and by Von Willebrand factor. The receptor site at the platelet is the glycoprotein Ib (GP I b) which is the primary target for this factor ***(Sakariassen et al., ١٩٨٦).***

Platelets undergo a shape change and spread out to cover more of the thrombogenic surface. Adherent platelets release Adenosine diphosphate (ADP) and thromboxane A_2 (TxAs), these substances are involved in the activation of non stimulated platelets (Fig. ٢) ***(Stein et al., ١٩٨٩).***

Glycoproteins (GP II b and GP III a) on the surface of platelet thus activated and bind tightly to fibrinogen. The activated (GP II b/III a), complex is termed the "fibrinogen receptor" so adherence requires platelet activation, adsorption of fibrinogen into the surface which is also essential for the

process of platelet to platelet binding that occurs during irreversible aggregation, and the presence of platelet membrane fibrinogen receptors, Von Willebrand factor is also critical to platelet adhesion and therefore is critical for the arrest of bleeding ***(Roth, ١٩٩١).***

Fig. (٢): Platelet function. The phases of platelet involvement in the early stage on thrombus formation are shown. Platelets initially adhere to subendothelial proteins such as collagen and Von Willebrand factor. They undergo a shape change, spread out, and release adenosine diphosphate (ADP) and thromboxane A_2 (TxA_2), which attract and activate other platelets, causing aggregation. Thrombus formation is completed by the formation of cross-linked fibrin strands. Endogenous inhibitors of thrombosis are shown ***(Stein et al., ١٩٨٩).***

Platelets contain three types of granules, dense, alpha and lysosomes. The **dense** granules contain adenosine diphosphate (ADP), adenosine triphosphate (ATP), inorganic phosphate and

serotonin. **Alpha** granules contain multiple proteins, including coagulation factors, platelet specific proteins such as platelet-derived growth factor, and the glycoproteins. Lysosomes contain acid hydrolyses ***(O'Reilly, ١٩٩٨).*** Thrombin and collagen induce secretion of substances from all three granule types, while epinephrine, ADP, and TxA_2 induce secretion from alpha and dense granules only. All these contents particularly ADP induce further platelet aggregation. Activated platelets also secrete TxA_2, which is a powerful platelet activator and aggregant ***(Spiess and Change, ١٩٩٣).***

Although thrombin is a powerful inducer of platelet aggregation, and stimulates synthesis of TxA_2, which induces thrombogenesis and vasoconstriction, it stimulates the synthesis of prostacyclin (PGI_2) from vessel wall, which inhibits thrombogenesis and causes vasodilatation. Under physiologic conditions the ratio of PGA_2 to TxA_2 is around ٤: ١. This is responsible at least in a part for maintaining endothelial thromboresistance and hemocompatibility ***(Havel et al., ١٩٩٢).***

Platelet plug quickly arrests bleeding but must be reinforced by fibrin for long-term effectiveness. Fibrin reinforcement results from local stimuli to blood -coagulation, the exposed collagen of damaged vessel, the membranes and released contents of platelets ***(O'Reilly, ١٩٩٨).***

Blood Coagulation System: