STUDY OF
SOME HAEMOSTATIC PARAMETERS
DURING ACUTE ATTACK OF HAEMATEMESIS
IN
CHRONIC LIVER DISEASES

Thesis

Submitted in Partial Fulfillment For

MASTER DEGREE
(GENERAL MEDICINE)

BY

ASHRAF M. Muhammed ALY BELAL

M.B., B.CH,

SUPERVISORS

Prof.Dr. Soheir Sheir

Prof.of Internal Medicine
Ain Shams University

Prof.Dr. Sawsan A Omran

Prof.of CLINICAL PATHOLOGY
Theodor Bilharz Resarch Institute

Prof.Dr. Abdel Moniem Tawfik

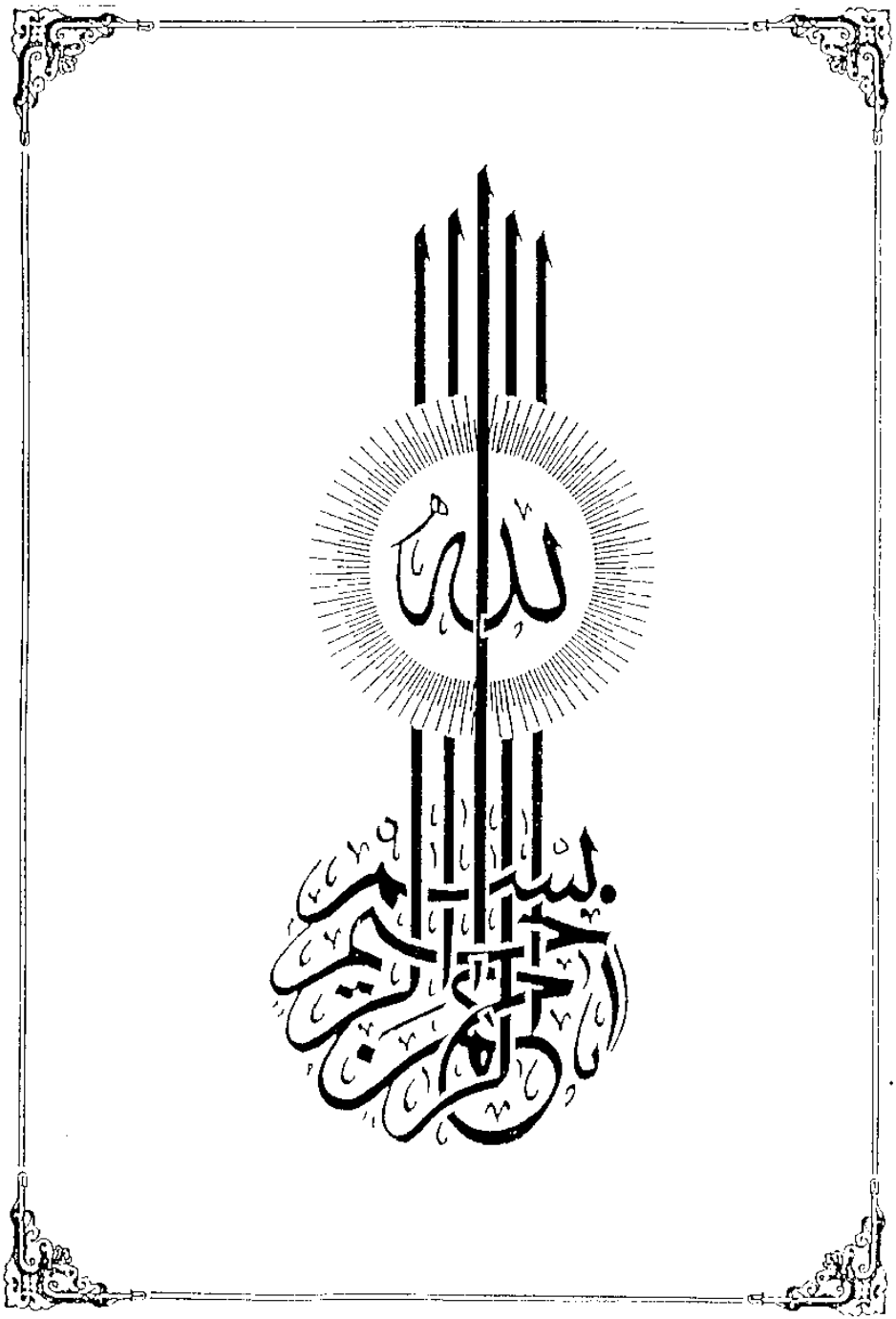
Prof.of GASTROENTEROLOGY
Military Medical Academy

Prof.Dr. Hebatalla Sedky

Asst.Prof.of Clinical Pathology
Ain Shams University

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY
1992

بسم الله الرحمن الرحيم



ACKNOWLEDGEMENT

I wish to express my sincere gratitude to Prof. Dr. **Soheir Sheir**; for her constant guidance, valuable advise and continuous support, without her creation and encouragement this work would have not been fulfilled.

I would like to express my deepest gratitude to Prof. Dr. **Abdel Monaem Tawfik Hussein.** Thanks a lot to him for his close supervision and continuous guidance.

I am also very grateful to Prof. Dr. **Sawsan A. Omran** to which the spirit of this deed in indeed credited to. Her wise guidance has enabled me to finish this work.

I may convey my gratitude to Prof. Dr. **Hebat Allah Adel Sedky** for her creative guidance and help.

I would like to thank Dr. **Fayza El Essawy** and Dr. **Nora El Bassiouny** , lecturar staff of clinical pathology theudor Bilahrz research institute for their help.

I would like to express my gratitude to Prof. Dr. **Ahmed Masoud** for his cooperation.

ASHRAF BELAL

LIST OF CONTENTS

INTRODUCTION AND AIM OF THE WORK ..... 1 - 2

- Review of Literature 3

HAEMOSTATIC MECHANISM ..... 3 - 19

- Vascular Phase 4
- Platelet Phase 5
- Plasma Phase 6
- Coagulation Sequence 7
- Natural Inhibitors of Coagulation 11
- Fibrinolytic System 13
- Activators of Fibrinolysis 15
- Inhibitors of Fibrinolysis 16

ROLE OF LIVER IN HAEMOSTASIS AND HEMOSTATIC ABNORMALITIES IN CHRONIC LIVER DISEASE ..... 20 - 38

- Defects of Blood Coagulation Factors 22
- Abnormalities of the Naturally Occurring Anticoagulants..26
- Abnormal Activity of the Fibrinolytic System 27
- Consumption Coagulopathy In Liver Cirrhosis 32
- Platelet Defects 35

BLEEDING OESOPHAGEAL VARICES AND HAEMOSTATIC MECHANISM ..39 - 43

MATERIALS AND METHODS .....44 - 63

RESULTS ..... 64 - 84

DISCUSSIONS ..... 85 - 89

SUMMARY .....90 - 92

REFERENCES ..... 93 - 114

INTRODUCTION AND AIM OF THE WORK

Bleeding from oesophageal varices is one of the most life threatening complication in patients with chronic liver disease (Paquet 1983).

The morality rate of the first attack of haematemesis in bilharzial hepatic fibrosis ranges between 50 - 60% and the five years survival rate is less than 10% (Graham & Smith; 1981).

Viral hepatitis compete nowadays with schistosomiasis as a leading cause of chronic liver disease in the Middle East (Nooman & Hassan; 1984).

Hepatitis BSAg was found more frequently in patients with hepatosplenic schistosomiasis (Hassanin et al; 1989).

The coexisting chronic hepatitis B is a major cause of clinical decompensation in bilharzial patients with cirrhosis.

Variceal bleeding and ascites were all shown to be accelerated in the presence of mixed infection (Abdel Wahab and Mahmoud 1987).

The liver plays an important role in maintaining the normal haemostatic mechanism. It is the site of synthesis of fibrinogen , plasminogen and blood coagulation factors. (Al Mofleh et al 1989).

The liver also is the site of clearance of plasminogen activator and the site of synthesis of various plasminogen activator inhibitor as alpha 2 antiplasmin. (Saito et al 1982).

Severe hepatic cirrhosis is associated with complex haemostatic and coagulation defects : impaired hepatic synthesis of coagulation factors and accelerated fibrinolysis (Omran et al 1987 - Hersch et al ; 1987).

The aim of this work is to study some of the hemostatic parameters that might have a role in the pathogenesis of haematemesis in chronic liver diseases.

REVIEW OF LITERATURE

HAEMOSTATIC MECHANISMS

When the circulation is breached, a series of events takes place that lead to the formation of blood clot. This leads to sealing off of the blood vessel and prevents further blood loss.

The initial event is constriction of the blood vessel and formation of a temporary haemostatic plug of platelets.

This is followed by a cascade of reactions that lead to the formation of a fibrin clot (Kaplan et al; 1981).

The clotting mechanism is balanced by antithrombotic mechanisms that prevent clots from developing in uninjured vessels and maintain the blood in a fluid state (Ogston and Bannett; 1977).

The process of haemostasis will be divided into separate phases. These are vascular phase, platelet phase and plasma phase including coagulation sequence , the natural inhibitors of coagulation and the fibrinolytic system (Kaplan; 1978).

1. VASCULAR PHASE :

Blood vessels contribute in haemostasis through several mechanisms. Beyond the vasoconstriction which occurs in response to vascular injury, blood vessels have a role in keeping blood in a fluid state under normal conditions, and in haemostatic plug formation (Pearson et al; 1980 - Esmon et al; 1982 a).

Injury to the arterial circulation results in vasoconstriction, large arteries as well as arterioles contract promptly. The main value of vasoconstriction is to shunt blood away from the area of damage. The immediate response is mediated by Local axon reflex , then maintained by platelet release products including serotonin and thromboxane A_2 (Hamberg et al 1975 - Kaplan et al 1981).

Injury in the vessel wall causes marked rises in tissue factor activity and initiates coagulation via the extrinsic pathway (westen et al 1979). Also the exposed collagen and other subendothelial elements, along with aggregating platelets , create surface changes that activate factor XII and its dependent factors to trigger the intrinsic pathway of blood coagulation. (Kaplan et al 1981).

2. PLATELET PHASE :

The main function of platelets is to maintain haemostasis. Their action in haemostasis is three-folded. They react at de-endotheliated sites in the circulation to cover the denuded area and maintain the integrity of the vascular compartment.

Damage sufficient to breach the circulation results in stimuli which , in addition to causing adhesion , trigger a further series of reactions during which the platelet extrudes active agents to recruit other platelets into the haemostatic plug.

Where endothelial covering is incomplete , platelets adhere to collagenous and non collagenous elements in the exposed subendothelium. Platelet - Collagen adhesion is the most important physiological adhesion reaction as this can lead to platelet - release reaction and platelet - aggregation (Gorden and Milner , 1986).

Following adhesion of platelets to the exposed subendothelium, platelets contract and extrude the contents of their granules. This process is initiated by collagen and thrombin.

Release of stored amines and synthesized prostanoids following adhesion of single platelet cause other platelets to become sticky and adhere to platelets undergoing release and to each other forming a haemostatic plug at the site of injury (Golden and Milner 1976).

The relation of platelets to blood coagulation occurs in two different ways. The most important is the Catalytic function which they provide in the generation of thrombin by the factor Xa complex prothrombinase activities and in the generation of activated factor X by the intrinsic pathway factor Xa - forming activities. Also platelets possess and inherent capacity to activate factors XII and XI.

3. PLASMA PHASE :

Plasma phase of the haemostatic process involves coagulation sequences - natural inhibitors of coagulation and the fibrinolytic system.

A. COAGULATION SEQUENCE :

The coagulation mechanism involves two main pathways which provide alternative routes for generation of active factor X and the final common pathway of thrombin formation.

- Intrinsic Pathway :

In which all coagulation factors are related to blood. (Kaplan et al ; 1981).

- Extrinsic Pathway :

In which tissue factor plays a role (poller , 1977).

- The Intrinsic System :

Activation of the intrinsic system occurs when blood comes into contact with non-endothelial surfaces , such as collagen (Niewiarowski et al ; 1965).

Four factors are involved in the process of contact activation : Factor XII ,Factor XI , Prekallikrein ; and high molecular weight kininogen (H.M.W-K).

Factor XII adsorbs to the foreign surface and this induces a conformational change in the molecule (Kaplan et al ; 1981).

Prekallikrein and **HMW-K** latch on the exposed surface in a one to one molar complex. Surface - bound **HMW-K** catalyses the production of Kallikrein from prekallikrein and Kallikrein cleaves factor XII , rendered susceptible to attack by surface binding (Cochrane and Griffin; 1979 - Kaplan ; 1978).

HMW-K provides a further key function in securing the binding and alignment of factor XI in the series of surface - bound reactions (Meier; 1977 - Cochrane and Griffin ; 1979).

Activated factor XII acts on factor XI converting it to an activated factor XI in a reaction accelerated by **HMW-K**. (Davies and Mc Nicol 1985).

Activated factor XI in a calcium - dependant reaction splits factor IX which is changed to an activated form (Meier ; 1977).

Factor X , the first molecule in the common pathway is activated by a complex consisting of activated factor IX, factor VIII , calcium and phospholipid. (Baugh and Hougie; 1977).

- THE EXTRINSIC SYSTEM :

The extrinsic system aims to provide an extremely rapid response to injury and augment thrombin generation by the more ponderous but quantitatively important intrinsic system. (Pitney , 1977).

The components of the extrinsic system are the tissue factor and factor VII. Tissue factor is released at the site of injury from the intima of blood vessels (Zeldis et al ; 1972).

Factor VII may be circulating in an enzymatically active form (Jesty & Nemerson ; 1974) and this accounts for the rapid response of the extrinsic system.

Factor VII and tissue factor bind rapidly to form a complex with calcium. This complex acts as a cofactor to convert factor X to factor Xa (Williams ; 1983).