UPDATES IN HAEMOSTASIS IN LIVER DISEASE

Essay

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Aim of the work

The aim of this work is to revew the updates in haemostasis and liver disease as regard etiology, pathophysiology, clinical picture, diagnosis and treatment and emphasizing the multifaceted aspects of coagulation disorders in liver disease from bleeding to hyper-coagulable states.

LIST OF APPREVIATIONS

mRNA……Messenger RNA.

ADP……Adenosine diphosphate.

GTP……Guanosine triphosphate.

PT……Prothrombin time.

aPTT……Partial throboplastin time.

TFPA……..Tissue factor pathway inhibitor.

AT……..Antithrombin.

SERIN……Serine protease inhibitor.

NO……..Nitric oxide.

t-PA……Tissue- type plasminogen activator.

PAI-1……Plasminogen activator inhibitor 1.

TFPA……Tissue factor pathway inhibitor.

APC……Activated protein C.

ECs……Endothelial cells.

INR……International normalized ratio.

TEG……Thromboelastography.

ROTEM……..Rotation thromboelastometry.

NASH……Nonalcoholic steatohepatitis.

HSC……Hepatic stellate cells.

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HCC……Hepatocellular carcinoma.

HVPG……Hepatic venous pressure gradient.

ADH……Antidiuretic hormone.

SBP……Spontaneous bacterial peritonitis.

AF…….Ascitic fluid.

HRS…….Hepatorenal syndrome.

GABA……..Gamma-aminobutyric acid.

CPT……..Child-Pugh-Turcotte.

MELD……Model for End Stage Liver Disease.

UNOS…….United Network of Organ Sharing.

RES……Reticuloendothelial system.

TAT……..Thrombin-antithrombin complex.

PPIC……Plasmin–plasmin-inhibitor complex.

TAFI……Thrombin-activatable fibrinolysis inhibitor.

AICF…….. Accelerated Intravascular Coagulation and Fibrinolysis.

vWF……Von Willibrand factor.

PS……... Protein S.

AICF…….Accelerated Intravascular Coagulation and Fibrinolysis.

CLD……Chronic liver disease.

NIEC……North Italian Endoscopic Club.

DIC……Disseminated intravascular coagulation.

PVT……..…..portal vein thrombosis.

BCS……Budd-Chiari syndrome.

HAT……..Hepatic artery thrombosis.

DVT…….Deep venous thrombosis.

PE……...……Pulmonary embolism.

PARs……..…….protease-activated receptors.

CVVH…….Continuous venovenous hemodialysis.

ECC……..……extracorporeal circuit.

NAFLD……...…… Non alcoholic fatty liver disease.

TTP…….……..….thrombotic thrombocytopenic purpura.

TMA…….……..Thrombotic microangiopathy.

PFA-100…….platelet function analyser-100.

MELD……model of end stage liver disease.

MNPT……..mean normal prothrombin time.

ISI…….international sensitivity index.

FFP…… .. fresh frozen plasma.

FP24……fresh frozen plasma 24 hours.

TRALI…….……..transfusion related acute lung injury.

rfVIIa ……..…..activated recombinant factor VII.

TPO……Thrombopoietin receptor agonists.

DDAVP……Deamino-8-d-arginine vasopressin.

AASLD…….American Association for the Study of Liver Disease.

NASH……..non alcoholic steatorrhea.

PNH……..… Paroxysmal nocturnal haemoglobinuria.

SCD…….…..……. Sickle Cell Disease.

MPNs……myeloproliferative neoplasms.

CML……chronic myeloid leukemia.

PV……..……polycythemia vera.

PMF……. Primary Myelofibrosis.

HL……..……. Hodgkin Lymphoma.

NHL……... Non-Hodgkin Lymphoma.

ALL……..…acute lymphoblastic leukemia.

AML……..acute myeloid leukemia.

CLL…… Chronic lymphocytic leukemia.

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INTRODUCTION

Patients with liver disease frequently acquire a complex disorder of hemostasis secondary to their disease. Routine laboratory tests such as the prothrombin time and the platelet count are frequently abnormal and point to a hypocoagulable state. With more sophisticated laboratory tests it has been shown that patients with liver disease may be in hemostatic balance as a result of concomitant changes in both pro- and antihemostatic pathways.**(Lisman and Porte, 2010)**

The liver is the site for synthesis of the vast majority of proteins that play a central role in maintaining hemostasis, by participating in the regulation of coagulation and fibrinolysis. Hepatocellular damage in patients with severe liver disease can lead to abnormalities in the production and function of coagulation and fibrinolytic factors, disrupting the balance between coagulation and anticoagulation systems. Result in hemostatic abnormalities(eg.impaired synthesis of clotting factors, heightened fibrinolysis, disseminated intravascular coagulation,thrombocytopeni ,andplateletdysfunction**(Radosavljevic, 2007)**

As the liver is the site of production of both the pro-coagulant and anticoagulant proteins, and also of the degradation of these proteins, the disruption in the balance of pro-coagulant proteins such as tissue factor, factor VII, factor X, and the von Willebrand factor compared with the rate of breakdown of the innate anticoagulant molecules such as protein C, protein S, and antithrombin III leads to dysfunction of hemostasis and clinically evident disturbances in both bleeding and clotting in liver disease. Although incidence figures are limited, some patients develop a

hyperfibrinolysis syndrome, while others have systemic and splanchnic thrombotic problems.**(Caldwell.et al, 2006)**

The treatment and prophylaxis of these disorders influence much of the medical decision-making in hepatic patient. It is well-known that the Child-Pugh score and the model for end-stage liver disease (MELD), both of which are prominently influenced by measures of coagulopathy, are predictive of mortality in liver disease**.(Merion. et al,2006)**

Relatively little is known about the pathophysiology of the coagulation defects of end-stage liver disease. Because traditional notions of the clotting cascade do not adequately explain bleeding risks and thrombotic events in cirrhosis patients, long-standing beliefs about hemostasis have been supplanted by newer theories on hemostasis in liver disease**.(Tripodi et al, 2006).**

NORMAL HEMOSTASIS

Understanding of blood clotting is intimately tied to the history of civilization. With the advent of writing 5000 years ago, it could be argued that the first symbols used for blood, bleeding, or clotting represented the first published coagulation pathway. The ancient peoples of the world always held blood in utmost mystical esteem. Through the ages, this esteem has been transmitted to modern times in the many expressions that use “blood,” such as “blood is thicker than water,” “blood of our fathers,” and others **(Lefkowitz ,2009).**

There is no universally accepted definition of hemostasis. The most simplistic definition is the “cessation of bleeding” An alternative one-dimensional view is the mechanistic concept that hemostasis represents the platelet and coagulation cascades involved in the cessation of bleeding. A more

refined clinical definition of hemostasis is bleeding control without the induction of pathologic thrombotic events such as myocardial infarction, stroke, arterial thrombosis, or deep vein thrombosis **(Levy et al,2010).**

Hemostasis can be considered as control of bleeding within the finely tuned balance of procoagulant, anticoagulant, fibrinolytic, and antifibrinolytic activities and involves a complex interaction between both cellular and molecular components **(Eyre & Gamlin**, **2010).**

Vessel-wall injury and the extravasation of blood from the circulation rapidly initiate events in the vessel wall and in blood that seal the breach. Circulating platelets are recruited to the site of injury, where they become a major component of the developing thrombus; blood coagulation, initiated by tissue factor, culminates in the generation of thrombin and fibrin. These events occur concomitantly and temporally in four overlapping stages. **(Furie&Furie, 2008)** .