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Coagulation Disturbances In Liver Transplant Patients

Essay
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Shimaa Mostafa Ismael Mostafa Alsharef

Contents

List of Abbreviations

µg.....	Microgram.
ADP	Adenosine diphosphate.
APC	Activated protein C.
aPTT	Activated partial thromboplastin time.
AT	Antithrombin.
CFT	Clot formation time.
CI	Cardiac index.
CLI.....	Reduced clot lysis index .
CT	Clotting time.
DCD.....	Expanded criteria donors.
DDAVP ...	Deamino-8-d-arginine vasopressin.
DIC	Disseminated intravascular coagulation.
DO2.....	Oxygen Delivery.
DTI.....	Direct thrombin inhibitors.
DVT	Deep venous thrombosis.
EACA	Epsilon aminocaproic acid.
EBL.....	Estimated blood loss.
ECPR	Endothelial cell protein C receptor.
ELT	Euglobulin lysis time
ESLD	End stage liver disease.
factor VIIa	Activated factor VII
FDPs	Fibrin degradation products.
FFP	Fresh frozen plasma.
HAT.....	Hepatic artery thrombosis.
HIT.....	Heparin induced thrombocytobenia.
HLA.....	Human leukocyte antigen.
HLE.....	Heparin-like effect .
i.v	Intravenously.
ICT	Intracardiac thrombosis.
IL-6.....	Interleukin 6.
INR	International Normalized Ratio.
IPF	initial poor function.
ISI	International sensitivity index.

List of Abbreviations (Cont.)

ITP ..... Idiopathic immune thrombocytopenia.
Kg ..... Kilogram.
KIU ..... Kallikrein inhibitory units.
LDLT ..... Living donor liver transplantation.
LMWH .... Low molecular weight heparin.
LOT..... Lysis onset time.
LT ..... Liver transplatation.
MCF..... Maximum Clot firmness.
MCFext ... Extrinsic Maximum Clot firmness.
MELD ..... Model of End-Stage Liver Disease.
mg/dL..... Millligram per deciliter.
ML ..... Maximum Lysis.
NHBD ..... Non-heart-beating donors.
OLT..... Orthotopic liver transplantation.
PAI-1..... Plasminogen activator inhibitor-1.
PAI-2..... Plasminogen activator inhibitor-2.
PAIgG ..... Platelet-associated immunoglobulins.
PARs ..... Protease activated receptors.
PCC..... Prothrombin complex concentrate.
PE ..... Pulmonary embolism.
PF4…….. ...Platelet factor 4.
PNF……Primary nonfunction.
PT ..... Prothrombin time.
PZ ..... Protein Z.
RB ..... Reticulate body.
RBC ..... Red Blood Cell
rFVIIa ..... Recombinant activated factor VII.
RT ..... Reptilase time.
SD ..... Solvent/Detergent process.
SVRI ..... Systemic vascular resistance index.
TA..... Tranexamic acid.
TAFI ..... Thrombin activatable fibrinolysis inhibitor.
TAT ..... Thrombin–antithrombin.

List of Abbreviations (Cont.)

TEG..... Thromboelastography.
TF ..... Tissue factor.
TFPI ..... Tissue factor pathway inhibitor.
TIPS ..... Transjugular intrahepatic portosystemic shunt.
TNFα ..... Tumour necrosis factor-alpha.
tPA ..... Tissue-type plasminogen activator.
TPO ..... Thrombopoietin.
TRALI ..... Transfusion-related acute lung injury.
TT ..... Thrombin time.
UFH ..... Unfractionted heparin.
UNOS ..... United Network For Organ Sharing.
uPA ..... Urokinase-type plasminogen activator.
VTE..... Venous thromboembolism.
vWF ..... von Willebrand factor.
WBCLT ... Whole blood clot lysis time.
ZPI ..... PZ-dependent protease inhibitor.
α2-PI Alpha2-antiplasmin

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Introduction

The liver is the second most commonly transplanted major organ, after the kidney, so it is clear that liver disease is a common and serious problem ***(Guillen et al., 2005)***.

In Egypt, the number of adult living donor liver transplantation (LDLT) performed annually has increased rapidly in the past few years **(Khalaf et al., 2005).**

Liver problems include a wide range of diseases, which may be inherited as Alpha-1-antitrypsin deficiency, Gilbert's syndrome Wilson's disease; or can occur in response to viruses as Hepatitis B and Hepatitis C or liver adenoma and cancer. Some liver problems are temporary and go away on their own, while others can lead to end stage liver disease and mandate liver transplantation ***(Michael et al., 2011).***

The liver plays several key roles in blood coagulation being involved in both primary and secondery hemostasis ***(Lisman et al., 2002).*** Liver is the site of synthesis of all coagulation factors and their inhibitors except for von wellebrand factor (vWF) ***(Rapaport, 2000).***

Liver damage is commenly associated with impairment of coagulation, when liver reserve is poor. The hemostatic system is in a delicate balance between prothrombotic and antithrombotic processes, aiming to prevent excessive blood loss from injured vessels and to prevent spontaneous thrombosis. Liver failure is accompaniedby multiple changes the hemostatic system, because of redeced plasma levels of procagulative and anticoagulative factors synthesised by hepatocytes and sinusoidal cells ***(Tripodi et al., 2005).***

Moreover, during liver failure, there is a reduced capacity to clear activated hemostatic proteins and protein inhibitor complexes from the circulation. Thus, the global

effect of liver disease with regard to hemostasis is complex, so that proteins with advanced liver disease can experience sever bleeding or even thrombotic complications ***(Senzolo et al., 2006).***

When end stage liver disease occurs, liver transplantation is the only way available to save such patients and correct genetic clotting defects, such as hemophilia or factor V leiden mutation. Although it is the only way to restore normal hemostasis, coagulation disturbances in liver transplantation are still the major perioperative problem in those patients ***(Arai et al., 1996).***

During liver transplantation, hemorrage may occure due to the preexisting hypocoagulable state, the collateral circulation caused by portal hypertention and increased fibrinolysis that occurs during this surgery ***(Senzolo et al., 2006).*** A patient in the postoperative period following liver transplantation undergoes drastic changes in the ability to synthesize proteins such as albumin and coagulation factors, transitioning from a state devoid of synthetic ability to a fully functioning graft ***(Anderegg et al., 2008).***

Aim Of The Work

This essay aims at reviewing the coagulation disturbances that may occur in liver transplant patients, underlying mechanisms and assessing how to diagnose, prevent and treat such coagulation problems in those patients.

COAGULATION DISTURBANCES IN HEPATIC PATIENTS

Liver plays a major role in hemostasis, as most of the coagulation factors, anticoagulant proteins and components of fibrinolytic system are synthesized by hepatic parenchymal cells. Additionally, the reticuloendothelial system of the liver helps to regulate coagulation and fibrinolysis by clearing these coagulation factors from the circulation. Liver is the primary site of synthesis of most of the clotting factors and the proteins involved in the fibrinolytic system including all vitamin K-dependent coagulation proteins (factors II, VII, IX, X, protein C, protein S and protein Z) as well as factor V, XIII, fibrinogen, antithrombin, α 2-p1 and plasminogen ***(Desancho and Pastores, 2007).***

A. Physiology of hemostasis

Normal hemostatic balance is dependent on a complex interplay between procoagulant, anticoagulant and fibrinolytic proteins. Initiation of coagulation begins when tissue factor (TF) exposed after an injury to the vessel wall **(Fig. 1-1**). Tissue factor forms complex with activated factor VII (factor VIIa) present in the plasma. The TF/factor VIIa complex converts factor X to factor Xa, which, in turn, along with a cofactor, factor Va, converts prothrombin (factor II) to thrombin (factor IIa) ***(Rosenberg and Aird, 1999).***

Although this process generates a small amount of thrombin, this thrombin serves to prime the coagulation cascade by increasing the enzymatic activity of factor VIIa, making it 100-fold more active. In addition, thrombin activates factor V, VIII, XI and platelets, which form the infrastructure to amplify the enzymatic reactions of the coagulation cascade. Ultimately, thrombin is formed directly by the TF/VIIa complex activating factor X to Xa or indirectly by converting

factor IX to factor IXa, which in turn complexes with its cofactor, factor VIIIa, to convert factor X to factor Xa ***(Esmon, 2003).***

The large amount of thrombin that is generated cleaves fibrinogen to fibrin monomers, which in turn spontaneously polymerize and are cross-linked by factor XIIIa (which itself is activated by thrombin) to produce a stable clot. At this time, thrombin activatable fibrinolysis inhibitor (TAFI) becomes fully active and serves to diminish the incorporation and activation of plasminogen, leading to delayed clot lysis. TF-dependent generation of thrombin is rapidly inhibited by TF pathway inhibitor (TFPI), which binds TF/VIIa/Xa forming the quaternary complex TFPI/Xa/TF/VIIa, which is internalized by the TF-bearing cell ***(Esmon, 2003)*** **(Fig.1- 2).**

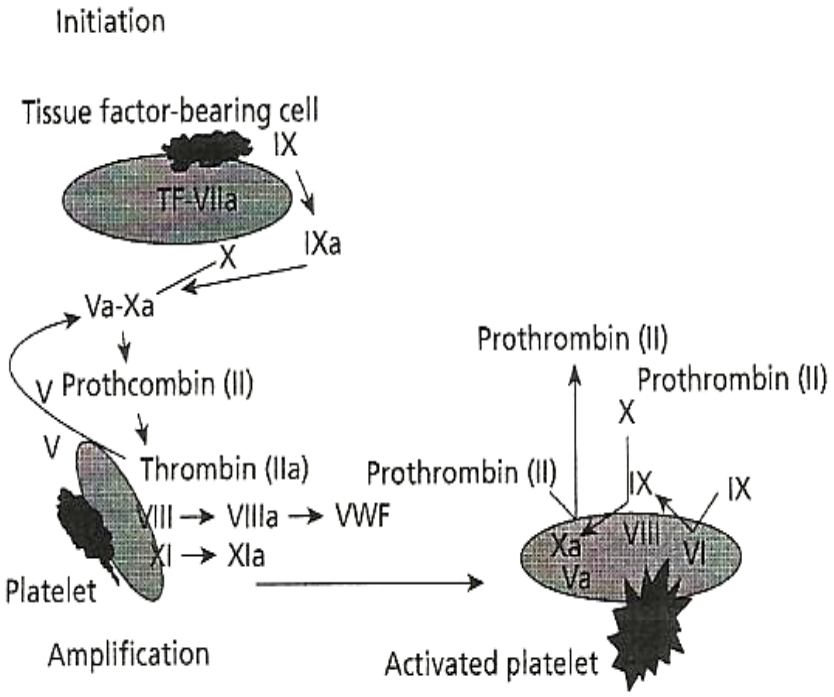

Fig.1-1: Tissue factor is the major initiator of coagulation ***(De sancho and Pastores, 2007).***

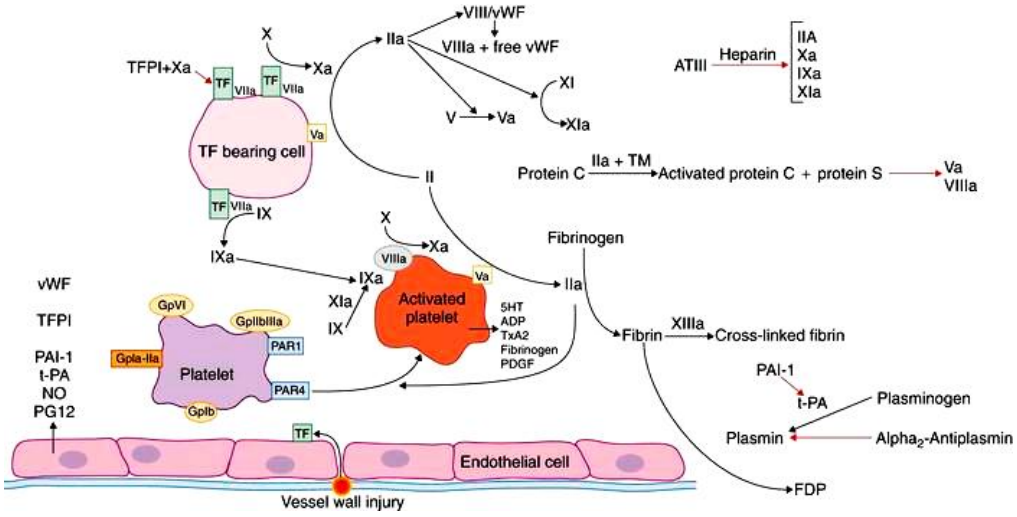

Fig.1-2: The fibrinolytic and natural anticoagulant ***(Baz and Mekhail, 2011).***

The main endogenous anticoagulant system is the protein C-dependent system. Protein C and its cofactor protein S are both vitamin K-dependent factors synthesized by the liver. Protein C binds to an endothelial cell protein C receptor (ECPR) and is activated by thrombin bound to thrombomodulin, an another endothelial cell membrane-based protein ***(Esmon, 2003).*** The activated protein C complex inactivates factors VIIIa and Va ***(Sofi et al., 2004)*** **(Fig. 1-2**).

Another important endogenous anticoagulant system involves antithrombin (AT), also primarily produced in the liver, which inactivates thrombin (IIa), factors Xa, IXa, XIa and XIIa. The anticoagulant activity of AT can be increased by up to 1000-fold in the presence of heparin ***(Sofi et al., 2004).***

Another vitamin K-dependent anticoagulant is protein Z, Protein Z (PZ) is a vitamin K-dependent plasma glycoprotein whose structure is similar to that of factors VII,IX,X, and proTein C ***(Ichinose et al., 1990; Sejima et al., 1990).*** In

contrast to these serine protease zymogens, however, PZ lacks the histidine and serine residues of the canonical catalytic site and does not serve aproteolytic function. Instead, PZ functions as a cofactor to enhance the inhibition of factor Xa by a serpin termed PZ-dependent protease inhibitor (ZPI) ***(Han et al., 1998; Han et al., 2000).***

In addition to inhibiting factor Xa in a PZ- dependent fashion, ZPI also inhibits factor XIa in the absence of PZ ***(Han et al., 2000).*** Finally,to prevent excess clotting, fibrin is digested by the fibrinolytic system, the major components of which are plasminogen and tissue-type plasminogen activator (tPA) **(Fig. 1-2).** Both these proteins are incorporated into polymerizing fibrin, where they interact to generate plasmin, which in turn acts on fibrin to dissolve the preformed clot. Plasminogen binds to fibrin at specific lysine binding sites and to tPA. The binding of plasminogen to tPA converts the proenzyme plasminogen to active proteolytic plasmin. Plasmin cleaves polymerized fibrin strands at multiple sites and releases fibrin degradation products (FDPs) ***(Sofi et al., 2004).***

The fibrinolytic system is regulated by three serine proteinase inhibitors: alpha2-antiplasmin (α2-PI), plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor-2(PAI-2) (**Fig. 1-2).** α2-PI is secreted by the liver, is present within platelets and serves to immediately inactivate free plasmin,whereas PAI-1 is the most important and most rapidly acting physiological inhibitor of both tPA and urokinase-type plasminogen activator (uPA)**.** Plasminogen activator inhibitor-2 (PAI-2), originally purified from human placenta, inhibits both two-chain tPA and two-chain uPA with comparable efficiency, but it is less effective towards single-chain tPA ***(Cesarman-Maus and Hajjar, 2005).***