Intensive Care Management of Liver Related Coagulation Disorders

Essay

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Abstract

Background: Blood coagulation is based on complex interactions between cells and plasmatic coagulation factors with elaborated feedback mechanisms including amplifying and inhibiting loops. It is best described by the term 'hemostasis', highlighting the sensible equilibrium between procoagulant and anticoagulant factors as well as fibrinolytic and antifibrinolytic mechanisms. The majority of plasma clotting factors and proteins of the fibrinolytic system and anticoagulants are synthesized in the liver, while cell surface factors responsible for heamostasis are not synthesized by liver.

Aims: The aim of this essay is to discuss management of liver related coagulation disorders in the intensive care unit.

Methodology: The liver plays a central role in hemostasis as it synthesizes nearly all circulating coagulation factors and inhibitors, as well as some of the components of the fibrinolytic system. The liver synthesizes thrombopoeitin, which is a hormone essential for stimulation of platelet production from megakaryocytes in the bone marrow. The liver diseases (whether acute or chronic) frequently are associated with complex alterations of the hemostatic system. The typical hemostatic profile of patients with advanced liver disease consists of decreased levels of nearly all proteins that promote or inhibit coagulation and fibrinolysis, thrombocytopenia, and platelet function defects. In contrast to most hemostatic proteins, levels of von Willebrand factor (VWF) are elevated due to enhanced production by the endothelium or reduced clearance by the liver.

Conclusion: The reduced portal blood flow and blood vessel damage may play an important role in the increased risk of portal vein thrombosis (PVT), but the hemostatic status may also contribute because patients with cirrhosis carrying the prothrombin G20210A mutation appear to have an increased risk for of portal vein thrombosis.

Keywords: Intensive Care Management, Liver Related Coagulation Disorders, Willebrand factor

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Contents

List of Abbreviations

13-HODE : 13-hydroxy octadecadienoic acid.
ADP : Adenosine diphosphate.
ADPase : Adenosine diphosphatase
APC : Activated protein C.
ATⅢ : Antithrombin Ⅲ.
CLD : Chronic liver disease.
DDAVP : 1-Deamino-8-D-arginine vasopressin.
DIC : Disseminated intravascular coagulopathy.
EDRF : Endothelium-derived relaxing factor.
ESLD : End stage liver disease.
FFP : Fresh frozen plasma.
FN : Fibrin network.
G-CSF : Granulocyte colony-stimulating factor.
GvHD : Graft versus host disease.
HCV : Hepatitis c virus.
HIV : Human immunodeficiency virus.
HLA : Human leukocyte antigens.
HPA : Human platelet antigen.
ICU : Intensive care unit.
IFN-a : Interferon alfa.
IgG : Immune globulin G.
IL : Interleukin.
INR : International normalization ratio.
ITP : Idiopathic immune thrombocytopenia.

IV : Intravenous.
PAF : Platelet activating factor.
PAI : Plasminogen activator inhibitor.
PAI-1 : Plasminogen activator inhibitor-1.
PAIgG : Platelet-associated immunoglobulins.
PC : Protein C.
PGE2 : Prostaglandin.
PGI2 : Prostacyclin.
PLG : Plasminogen.
PS : Phosphatidylserine.
PT : Prothrombin time.
TAFI : Thrombin activatable fibrinolysis inhibitor.
TEG : Thromboelestography.
TFPI : Tissue factor pathway inhibitor.
t-PA : Tissue plasminogen activator.
TPO : Thrombopoietin.
TPO-R : Thrombopoietin receptor.
TTP : Thrombotic thrombocytopenic purpura.
TXA : Tranexamic acid.
uPA : Urokinase plasminogen activator.
VWF : von Willebrand factor.
α2- PI : α2-plasmin inhibitor.

List of Figures

List of Tables

Introduction

Blood coagulation is based on complex interactions between cells and plasmatic coagulation factors with elaborated feedback mechanisms including amplifying and inhibiting loops. It is best described by the term 'hemostasis', highlighting the sensible equilibrium between procoagulant and anticoagulant factors as well as fibrinolytic and antifibrinolytic mechanisms ***(Schadena et al., 2013).***

The majority of plasma clotting factors and proteins of the fibrinolytic system and anticoagulants are synthesized in the liver, while cell surface factors responsible for heamostasis are not synthesized by liver ***(Caldwell et al., 2006).***

A myriad of altered coagulation parameters are readily measurable, such as thrombocytopenia, prolonged global coagulation times, reduced levels of coagulation inhibitors, or high levels of fibrin split products. Prompt and proper identification of the underlying cause of these coagulation abnormalities is required, since each

coagulation disorder necessitates very different therapeutic management strategies ***(Levi and Opal, 2006).***

Chronic or acute liver disease frequently have a profound impact on the hemostatic system. An important contributor to the coagulation disturbances in liver disease is decreased plasma levels of hemostatic proteins synthesized by the liver. In addition, thrombocytopenia as a result of decreased platelet production or increased platelet turnover and intravascular activation of hemostasis resulting in consumption of hemostatic factors contributes to alterations in the hemostatic system. Furthermore, continuous low grade activation of endothelial cells results in continuous release of several hemostatic proteins whose levels are therefore frequently elevated in patients with liver disease (eg, von Willebrand factor VWF). Finally, portal hypertension, a common complication of chronic liver failure, results in hemodynamic changes that may impact endothelial function. Moreover, portal hypertension results in splenomegaly, which in turn results in increased platelet sequestration in spleen ***(Lisman and Porte1, 2010).***

Impaired synthesis of coagulation factors is often due to liver insufficiency or vitamin K deficiency. The

prothrombin time is very sensitive to both conditions, since this test is highly dependent on the plasma levels of factor VII (a vitamin K-dependent coagulation factor with a short half-life). Liver failure may be differentiated from vitamin K deficiency by measuring factor V, which is not vitamin K dependent. In fact, factor V plays an important role in various scoring systems for severe acute liver failure **(*Bailey et al., 2003).***

Patients with liver disease may develop quantitative (thrombocytopenia) and/or qualitative platelet abnormalities (thrombocytopathies) such as impaired platelet adhesion and aggregation. The aetiology of thrombocytopenia in these patients is often attributed to splenic sequestration (hypersplenism), but may also occur as a result of platelet destruction mediated by platelet associated immunoglobulins (PAIgG) and impaired hepatic synthesis and/or increased degradation of thrombopoietin (TPO**) (*Sanjo et al., 2003*).**

Thrombocytopenia is a common complication in liver disease and can adversely affect the treatment of liver cirrhosis, limiting the ability to administer therapy and

delaying planned surgical/diagnostic procedures because of an increased risk of bleeding ***(Hayashi et al., 2014).***

Proteins C and S are vitamin K dependent glycoproteins synthesised mainly by hepatocytes. During acute or chronic liver disease, their concentrations decrease concomitantly with the other coagulation factors, but usually not below 20% of normal **(*Rios et al., 2005*).**

DIC is characterized by intravascular fibrin deposition due to activation of the clotting cascade, common laboratory features include a prolonged PT and PTT, low fibrinogen level, elevated fibrin-degradation product and D-dimer and thrombocytopenia **(*Mannucci and Vigano, 1982*).**

Therapy for hemostatic abnormalities of liver disease is needed only during variceal bleeding, surgery or before invasive procedures. As Intravenous vitamin K injection, fresh frozen plasma, platelet transfusion, cryoprecipitate containing factor VII, desmopressin, Recombinant activated factor VII ***(Senzolo et al., 2006*).**

Aim of the Essay

The aim of this essay is to discuss management of liver related coagulation disorders in the intensive care unit.