Coagulopathy Management in Liver Transplantation

Essay
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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
ورَسُولُهُ والْمُؤْمِنُونَ

صدق الله العظيم

سورة التوبة آية (105)

*First, thanks are all due to **Allah** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

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Osama Fawzy Abd El-hady Ibrahim

List of Contents

List of Abbreviations

ADP	:	Adenosine diphosphate
APTT	:	Activated partial thromboplastin time
Ca^{++}	:	Calcium ions
cGMP	:	Cyclic monophosphate
CTXA2	:	Thromboxane A2
DIC	:	Disseminated intravascular coagulation
DIC	:	Disseminated intravascular coagulation
DSE	:	Dobutamine stress echo
DVT	:	Deep vein thrombosis
GABA	:	g-aminobutyric acid
GFR	:	Glomerular filtration rate
HLE	:	Heparin-like effect
HMWK	:	High-molecular-weight kininogen
HPS	:	Hepatopulmonary syndrome
HRS	:	Hepatorenal syndrome
ICT	:	Intracardiac thrombosis
ICU	:	Intensive care unit
INR	:	International Normalized Ratio
ISI	:	International Sensitivity Index
IVC	:	Infrahepatic vena cava
IX	:	Chrimstmas factor, serine protease
LT	:	Liver transplantation
MAC	:	Minimum alveolar concentration
MCF	:	Maximum clot firmness
MELD	:	Mayo End-Stage Liver Disease
OLT	:	Orthotopic liver transplantation
PAI-1	:	Plasminogen activator inhibitor-1
PAP	:	Pulmonary artery pressure
PE	:	Pulmonary embolism
PFA-100	:	Platelet Function Analyzer-100

List of Abbreviations(Cont.)

PGI2	:	Prostaglandin
PL	:	Platelet membrane phospholipid
PPH	:	Portopulmonary hypertension
PRS	:	Postreperfusion syndrome
PT	:	Prothrombin time
PTT	:	Partial thromboplastin time
RBC	:	Red blood cell
RCTs	:	Randomized controlled trials
TEE	:	Transesophageal echocardiography
TEG	:	Thromboelastogram or thromboelastrometry
TF	:	Tissue factor
TFPI	:	Tissue factor pathway inhibitor
tPA	:	Tissue plasminogen activator
t-PA	:	Tissue plasminogen activator
TPO	:	Thrombopoietin
UCLA	:	University of California, Los Anglos
V/Q	:	Ventilation–perfusion
VII	:	Stable factor, serine protease
VVB	:	Venovenous bypass
XI	:	Plasma thromboplastin, antecedent serine protease
XII	:	Hageman factor a serine protease
XIII	:	Fibrin stabilizing factor, a transglutaqminase

List of Figures

Introduction

Transfusion of blood products is common in liver transplantation. It significantly influences patient outcomes and the viability of the transplanted organ. Severe bleeding in orthotopic liver transplantation (OLT) results from a combination of blood loss of surgical origin and diffuse bleeding that requires a systemic approach for treatment **(Sabate et al., 2012)**.

Advanced cirrhosis produces a complex balance between procoagulant and antihemostatic actionsthat is characterized by a decreased levels of hemostatic proteins, low synthesis of anticoagulants (ATIII, protein C), thrombocytopenia, increased level of von Willebrand factor and factor VIII, increased nitric oxide and prostacyclin as well as a subtle equilibrium between tissue plasminogen activator (t-PA) and Plasminogen activator inhibitor-1 (PAI-1) **(Tripodi et al., 2011)**.

There are limited correlations between conventional hemostasis and coagulation tests with bleeding during liver transplantation. The risks of bleeding and transfusion in liver transplantation seem to be determined by patient age, severity of liver disease according to the value of Model for End-stage Liver Disease, preoperative hemoglobin and plasma fibrinogen values **(Mangus et al., 2007)**.

Thromboelastogram or thromboelastrometry (TEG) can be used to monitor the risk of bleeding or of thrombosis which coexist during surgery and when empirical treatments are applied. In the cirrhotic patient the TEG pattern is characterized by decreases in maximum clot firmness (MCF), clotting time, and clot formation time that show good correlations with fibrinogen and platelets **(Tripodi et al., 2009)**.

Reduction of blood product requirements has been achieved in liver transplantation; however, the procedure may still be associated with massive bleeding **(Roulet al., 2011)**. There is no evidence of clinical improvement by prophylactic correction of clotting factors; however, decreased plasma fibrinogen levels influence blood product requirements**(Costa et al., 2011)**.

Concern about unwanted events is a major limitation of pro -phylactic therapy to normalize plasma fibrinogen levels, even if there has not been communicated any thrombosis or elevations of d-dimers related to hypofibrinogenemia correction**(Farriols Danes et al., 2008)**.

Criteria to identify patients who could benefit from prophylactic treatment has not been presented, because this effect not only depends on the preoperative patient condition but also on donor liver quality as well as surgical conditions during the hepatectomy and anhepatic stages **(McCluskey et al., 2006)**.

Guidelines for antifibrinolytic therapy are the clot firmness in TEG or, alternatively, when diffuse bleeding is detected, a fibrinogen value less than 1 g/L. Antifibrinolytic drugs must not be used in patients with a medical history of thrombotic events, acute liver failure, or biliary cirrhosis. Data on thromboembolic complications in OLT are inconclusive**(Molenaar et al., 2007)**.

Thrombin generation is limited in severe thrombocytopenia, so that it seems reasonable to administer platelets when active bleeding coexists with a platelet count below 50, 000/mm **(Tripodi et al., 2006)**.

A note of caution should be mentioned when administration of high volumes of hemoderivates and antifibrinolytics do not correct severe bleeding; a consumption coagulopathy with secondary fibrinolysis should be suspected. Treatment of these patients must be based on correcting the underlying cause, mostly related to tissue hypoxia due to critical hypoperfusion **(Gologorsky et al., 2007)**.

Aim of the work

To discuss the most recent trends in the management of coagulation in patients undergoing liver transplantation.

Anatomy of the Liver

The liver is the largest organ of the human body, weighs approximately 1500 g, and is located in the upper right corner of the abdomen. The organ is closely associated with the small intestine, processing the nutrient-enriched venous blood that leaves the digestive tract. The liver performs over 500 metabolic functions, resulting in synthesis of products that are released into the blood stream (e.g. glucose derived from glycogenesis, plasma proteins, clotting factors and urea), or that are excreted to the intestinal tract (bile). Also, several products are stored in liver parenchyma (e.g. glycogen, fat and fat soluble vitamins) ***(Bismuth, 1982).***

Almost all blood that enters the liver via the portal tract originates from the gastrointestinal tract as well as from the spleen, pancreas and gallbladder. A second blood supply to the liver comes from the hepatic artery, branching directly from the celiac trunk and descending aorta. The portal vein supplies venous blood under low pressure conditions to the liver, while the hepatic artery supplies high-pressured arterial blood***(Lewis and Gray, 2000).***

Since the capillary bed of the gastrointestinal tract already extracts most O_2, portal venous blood has a low O_2 content. Blood from the hepatic artery on the other hand, originates

directly from the aorta and is, therefore, saturated with O_2. Blood from both vessels joins in the capillary bed of the liver and leaves via central veins to the inferior caval vein ***(Sear,2002).***

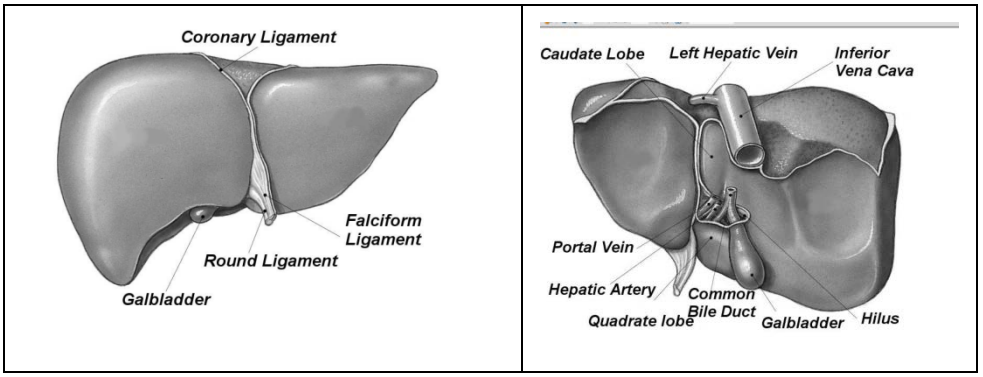

Figure 1: Anatomy of the liver ***(Agur and Lee and Grant ,1999).***

Basic liver architecture:

The major blood vessels (portal vein and hepatic artery), lymphatics, nerves and hepatic bile duct communicate with the liver at a common site, the hilus. From the hilus, they branch and rebranch within the liver to form a system that travels together in a conduit structure, the portal canal from this portal canal, after numerous branching, the portal vein finally drains into the sinusoids, which is the capillary system of the liver. Here, in the sinusoids, blood from the portal vein joins with blood flow from end-arterial branches of the hepatic artery. Once passed through the sinusoids, blood enters the collecting branch of the central vein, and finally leaves the liver via the hepatic vein. The hexagonal structure with, in most cases, three portal canals in its corners draining into one central vein, is defined as a lobule. The

lobule largely consists of hepatocytes (liver cells) which are arranged as interconnected plates, usually one or two hepatocytes thick. The space between the plates forms the sinusoid. A more functional unit of the liver forms the acinus. In the acinus, the portal canal forms the center and the central veins the corners. The functional acinus can be divided into three zones: 1) the periportal zone, which is the circular zone directly around the portal canal, 2) the central zone, the circular area around the central vein, and 3) a midzonal area, which is the zone between the periportal and pericentral zone ***(Parks et al., 2000).***

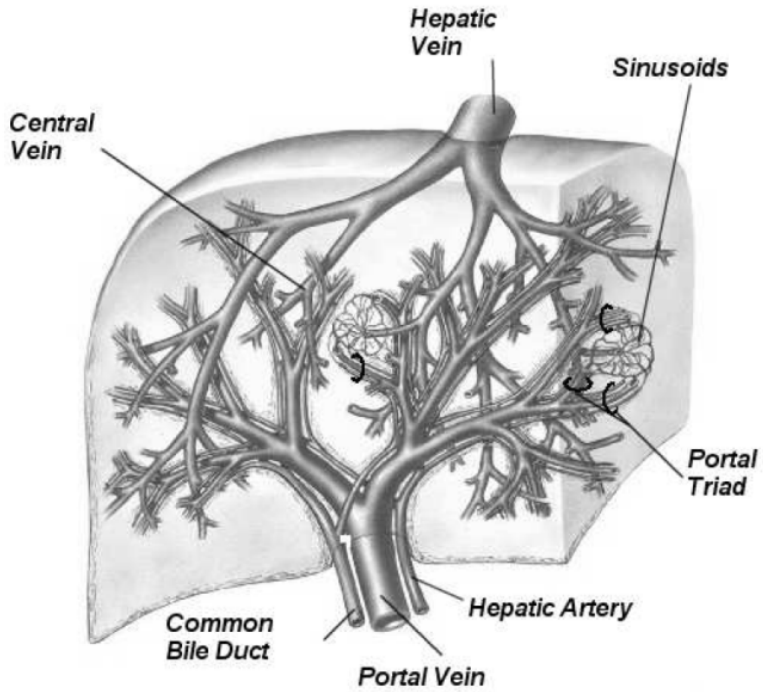

Figure 2: Network of branching and rebranching blood vessels in the liver***(Guyton,2006).***

Morphological Anatomy

The first description of the anatomy of the liver is what we can term the morphological anatomy, based on the surface features of the organ. On the anterior surface, the round ligament and the falciform ligament divide the liver into two lobes: the left and right lobes. On the inferior surface, the umbilical fissure, the gallbladder bed, and the hilus limit the quadrate lobe. Behind the hilus is the spigelian lobe. In total, there are two main lobes and two accessory lobes corresponding to the true definition of a lobe: "part of the parenchyma limited by fissures or grooves" (Stedman's Medical. Dictionary). However, this morphological description of the liver is inadequate to guide the surgeon in performing anatomical surgery ***(Strasberg,1997)***.

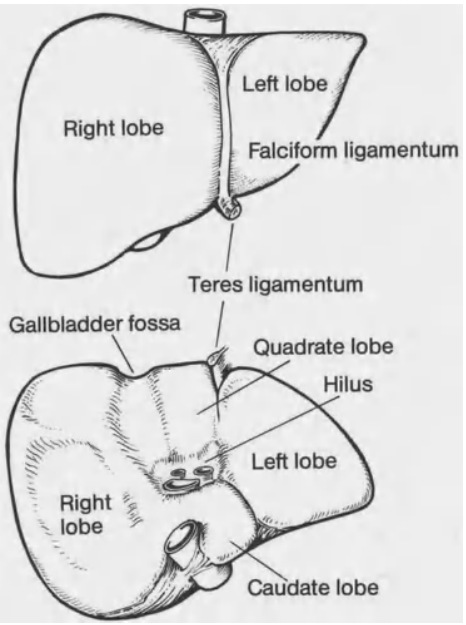

Figure 3: Morphology of the liver ***(Strasberg, 1997)***.