Recent advances in acquired coagulopathy in critically ill patient

Essay

Submitted for partial fulfillment of Master Degree
In Intensive Care Medicine

By
Hany Ramzy Zaki Ayaad
M.B., B.Ch

Supervised by

Prof. Dr. Sherif Wadie Nashed
Professor of Intensive Care Medicine and Anaesthesia
Faculty of Medicine-Ain Shams University

Dr. Heba Bahaa El-Din El-Serwi
Assistant Professor of Anaesthesia and Intensive Care Medicine
Faculty of Medicine-Ain Shams University

Dr. Mohamed Youssif Mohamed Khashaba
Lecturer of Anaesthesia and Intensive Care Medicine
Faculty of Medicine-Ain Shams University

Faculty of Medicine

Ain Shams University

2010

List of contents

List of Tables

List of abbreviations

DDAVP	1-desamino-8-D-arginine vasopressin
ACT	Activated clotting time
APTT	Activated partial thromboplastin time
APC	Activated protein C
ACoTS	Acute Coagulopathy of Trauma–Shock
ACS	Acute Coronary Syndrome
APL	Acute Promyelocytic Leukemia
ATLS	Acute Trauma Life Support
APSAC	Acylated plasminogen – streptokinase activator complex
ATP	Adenosin Triphosphate
ADP	Adenosine diphosphate
AMP	Adenosine monoiphosphate
AC	Adenylate cyclase
APLAS	Antiphospholipid Antibody Syndrome
AT	Antithrombin
ATIII	Antithrombin III
RGD	ARginine-Glycine-aspartate
ANP	Atrial natriuretic peptides
B.U	Betheda unit
CFT	Clot Firmness Time
CABG	Coronary Artery Bypass Graft
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DS	Danaparoid sodium
DVT	Deep Vein Thrombosis
DCP	Des-gamma-carboxy prothrombin

DTIs	Direct Thrombin inhibitors
DIC	Disseminated Intravascular Coagulation
EAC	Endogenous Acute Coagulopathy
EPCR	Endothelial protein C receptor
EDRF	Endothelial-derived relaxing factor
EGF	Epidermal Growth Factor
EACA	Epsilon-aminocaproic acid
FDPs	Fibrin-Degradation Products
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FEIBA	FVIII Inhibitor Bypassing Activity
GM	Gabexate Mesilate
GPIIb/IIIa	Glycoprotein IIb/IIIa
GAG	Glycosaminoglycan
GMP	Guanosine monophosphate
HELLP	Hemolytic Anemia, Elevated Liver Enzymes and Low Platelet count Syndrome
HUS	Hemolytic Uraemic Syndrome
HIT	Heparin Induced Thrombocytopenia
HUVEC	Human Umbilical Vein Endothelial Cells
IL-1	Interleukin 1
INR	International Normalized Ratio
ISI	International Sensitivity Index
KIU	Kallikrein Inactivator Units
LR	Lactated Ringer's solution
LC	Liver cirrhosis
LMWH	Low-molecular-weight-heparins
MBL	Mannose Binding Lectin

MCF	Maximum clot firmness
MAPK	Mitogen Activated Protein Kinase
MW	Molecular wieght
MI	Myocardial Infarction
SNAC	N-(8-(2-hydroxybenzoyl) amino) caprylate
NM	Nafamstat Mesilate
NAPc2	Nematode Anticoagulant Peptide
NCX	Nitric oxide-releasing aspirin
NSTEMI	Non S-T elevating myocardial infarction
PCI	Percutaneous Coronary Intervention
PAD	Peripheral Arterial Disease
PDE	Phosphodiestrase Enzyme
PLC	phospholipase-C
PAI-1	Plasminogen Activator Inhibitor-1
PVT	Portal Vein Thrombosis
PG-I	Prostaglandin I
PAR-1	Protease Activated Receptor 1
PC	Protein C
PIVKA	Protein in VK absence
PS	Protein S
PCC	Prothrombin complex concentrate
PT	Prothrombin time
PSGL-1	P-selectin glycoprotein ligand 1
PE	Pulmonary Embolism
RCTs	Randomised controlled trials
rFVIIa	Recombinant activated factor VII
RT	Reptilase time
RoTEM	Rotation thrombelastogram analyzer

scuPA	single chain urokinase type plas minogen activator
STEMI	S-T elevating myocardial infarction
SAK	Staphylokinase
SPI	Synthetic or purified protease inhibitors
SAC	Systemic Acquired Coagulopathy
SIRS	Systemic Inflammatory Response Syndrome
TNK-t-P	Tenecteplase
TT	Thrombin Time
TAFI	Thrombin-activatable-fibrinolysis-inhibitor
TAT	Thrombin–Antithrombin
TEG	Thromboelastography
TE	Thromboembolism
TM	Thrombomodulin
TM	Thrombo-moduline
TTP	Thrombotic thrombocytopenic purpura
TXA2	Thromboxane A2
TP	Thromboxane receptor
TF	Tissue Factor
TFPI	Tissue factor pathway inhibitor
tPA	Tissue plasminogen activator
TGFβ	Transforming growth factor β
TIA	Transiant ischemic attack
TNF	Tumour Necrosis Factor
UFH	Unfractionated Heparin
VTE	venous thromboembolism
VK	Vitamin K
VKA	Vitamin K Antagonist
vWF	von Willebrand factor

Introduction

Disorders of hemostasis and thrombosis are frequently encountered in the ICU setting. Understanding the relevance of laboratory findings is essential in providing appropriate therapy. Various blood products and hemostatic agents are available to assist in the control of bleeding, and several different classes of anticoagulants are now available for use. Appropriate use of these agents maximizes therapeutic effect while minimizing complications. Use of fresh frozen plasma, cryoprecipitate, and other hemostatic agents should generally be reserved for those who have active bleeding, those undergoing invasive procedures, and those at high risk for bleeding because of their underlying diagnoses or because of associated hematologic derangements ***(Marks PW, 2009).***

Acquired Coagulation disorders in critically ill patients result from basic mechanisms: Vitamin K deficiency, Liver disease, consumption of factors, or inhibition of factor activity or fibrin polymerization. Unlike inherited disorders, acquired coagulation disorders are often characterized by multiple factor deficiencies as well as platelet defects (quantitative and qualitative) (***Bongard et al., 2008).***

Chronic liver diseases are associated with thrombocytopenia and/or thrombocytopathy, decreased synthesis of most coagulation factors and hyperfibrinolysis. Because of the above characteristics chronic liver disease has been identified until recently as the prototype of the acquired hemostasis abnormalities and the causal relationship between abnormal hemostasis tests and the risk of bleeding has become a paradigm ***(Tripodi A, 2010).***

Anticoagulant agents are often used for the prevention and treatment of a wide range of cardiovascular diseases. The most frequently used anticoagulants are heparin or its derivatives, vitamin K antagonists (such as warfarin or coumadin) and antiplatelet agents. The most important complication of treatment with anticoagulants is hemorrhage, which may be serious, may cause long-term debilitating disease, or may even be life-threatening. If severe bleeding occurs or if a patient needs to undergo an urgent invasive procedure, such as emergency surgery, it may be necessary to reverse the anticoagulant effect of the various agents. Depending on the clinical situation, i.e., the severity of the bleeding or the urgency and estimated risk of the invasive procedure, this reversal may take place over a few hours, but in some cases immediate reversal is necessary ***(Levi M, 2009).***

Disseminated intravascular coagulation **(DIC)** is generally considered to be characterized by intravascular activation of coagulation with the loss of localization, which mainly occurs in the small veins and arteries due to various causes. The most common underlying diseases in patients with **DIC** are leukemia, infectious diseases, solid cancer, obstetric complications and aortic aneurysms. It may be classified as follows: asymptomatic type, marked bleeding type, and organ failure type. Although treatment of **DIC** is important, adequate treatment differs according to type of **DIC** ***(Wada H et al., 2010).***

Abnormal coagulation parameters can be found in 25% of *trauma* patients with major injuries. Furthermore, trauma patients presenting with coagulopathy on admission have worse clinical outcome. Tissue trauma and systemic hypoperfusion appear to be the primary factors responsible for the development of acute traumatic coagulopathy after injury. This coagulopathy can then be exacerbated by subsequent physiologic and physical derangements such as consumption of coagulation factors, haemodilution, hypothermia, acidemia and inflammation, all factors being associated with ongoing haemorrhage and inadequate resuscitation or transfusion therapies ***(Ganter M and Pittet J 2010).***

Chapter 1

Physiology of Hemostasis

Hemostasis is a highly adaptive process that control blood fluidity, and rapidly induces hemostatic plug formation after vascular injury, in order to stop or limit bleeding. After an initial triggering event, sequential steps occur, including a complex cascade of clotting factor and platelet activation. Red blood cells, leukocytes and endothelial cells are also involved in the propagation and the regulation of clot formation ***(Lasne et al., 2006).***

Moreover, the coagulation system is not only made for forming clots but is also involved in a variety of defense systems against micro-organisms, autoimmune processes, arteriosclerosis, tumour growth and metastasis. The main cellular components of the coagulation system are platelets, endothelial cells, monocytes and erythrocytes, and the main molecular components are the coagulation factors and inhibitors, fibrinolysis factors and inhibitors, adhesive proteins (e.g. von Willebrand factor), intercellular protein, acute-phase proteins, immunoglobulins, calcium ions, phospholipids, prostaglandins, and certain cytokines ***(Bombeli and Sphan, 2004)***.

Knowledge of the coagulation system continues to evolve from early concepts of zymogen clotting factors and cofactors activating and cofactors activating in sequence through two separate pathways, intrinsic and extrinsic to generate fibrin for clotting, to a more encompassing process that includes the vascular endothelium, blood coagulation, prevention of clotting and fibrinolysis. The fundamental principle that governs the coagulation system is the unremitting drive to balance procoagulant and anticoagulant forces. ***(Oliver WC, 2009).***

The term ***Hemostasis*** means prevention of blood loss, either by the physiological properties of vasoconstriction and coagulation or by surgical means. ***(Colman RW, 2006).***

Mechanisms of Hemostasis:

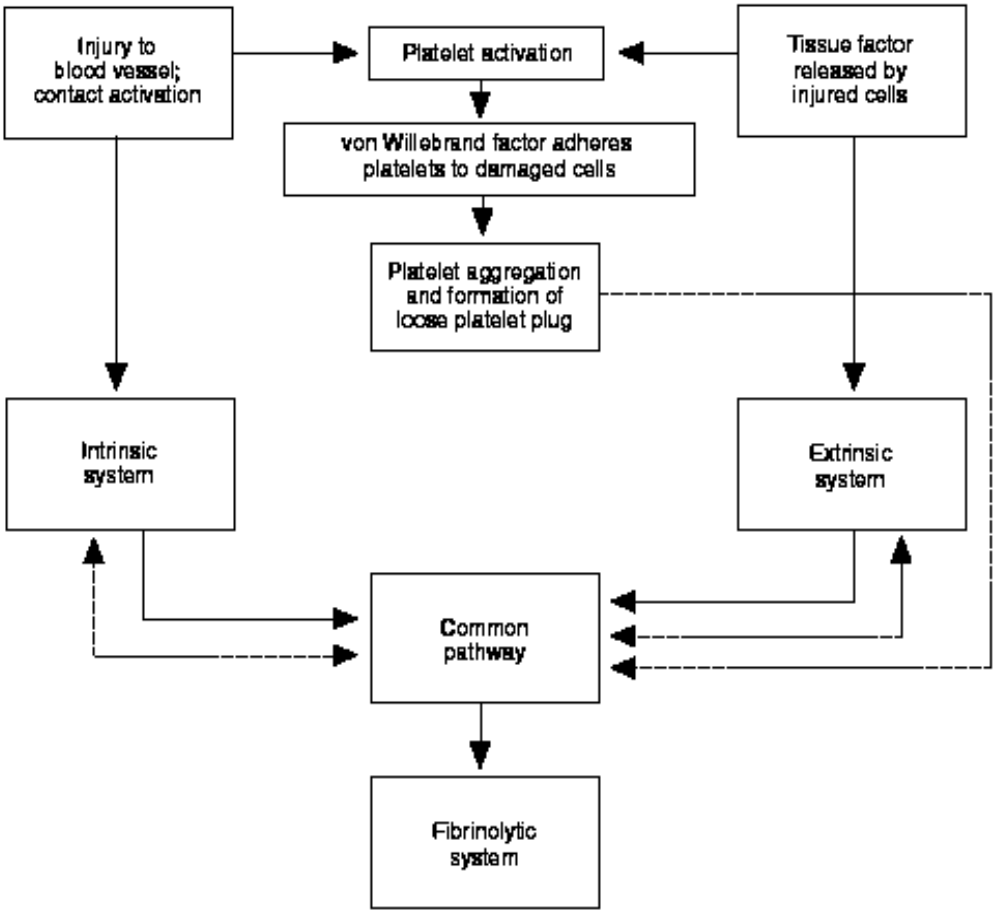
1- Vascular constriction.

2- Formation of a platelet plug.

3- Formation of a blood clot.

4- Eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

(Guyton and Hall, 2006)



(Figure1-1): **The coagulation an overview *2005 American Association of Clinical Chemistry.***

1- Vascular constriction:

Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the smooth muscle in the wall to contract; the contraction results from:

a) Local myogenic spasm.

b) Local autacoid factors from the traumatized tissues and blood platelets.

c) Nervous reflexes are initiated by pain impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues.

The more the severely a vessel is traumatized, the greater the degree of vascular spasm. The spasm can last for many minutes or even hours, during which time the processes of platelet plugging and blood coagulation can take place. ***(Guyton and Hall, 2006)***

However, a number of physiological derived compounds appear to induce vasoconstriction of a transient nature at the site of vascular injury. These include participation of endothelin, a very potent vasoconstrictor which is synthesized by endothelial cells, thromboxane A_2 (**TXA_2**), serotonin and the α-adrenergic system. Thrombin, thromboxane A_2 **IL-1**), transforming growth factor β (**TGFβ**), angiotensin II and epinephrine promote the expression of the endothelin mRNA, whereas shear stress, atrial natriuretic peptides (**ANP**) and brain natriuretic peptides negatively modulate its expression. Endothelial-derived relaxing factor (**EDRF**), an inhibitor of platelet function, inhibits release of endothelin ***(Arthur SB, 1998).***