Coagulation Disorders in Critically Ill Patient

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ
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Mohamad Mostafa Abo-Zeid Abdel-Aleem

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List of Abbreviations

ACCP	:	American College Of Chest Physicians
ACT	:	Activated Clotting Time
ADP	:	Adenosine Diphosphate
ADPase	:	Adenosine Diphosphatase
AHA	:	Acquired Hemophilia A
anti-TNF	:	Anti-Tumor Necrosis Factor
APC	:	Activated Protein C
aPCR	:	Activated Protein C Resistance
aPTT	:	Activated Partial Thromboplastin Time
ARB	:	Angiotensin Receptor Blocker
AT	:	Antithrombin
BNP	:	Brain Natriuretic Peptide
BU	:	Bethesda units
cAMP	:	Cyclic Adenosine Monophosphate
CTPA	:	Computed Tomographic Pulmonary Angiography
DDAVP	:	Desamino-8-D-arginine vasopressin
DIC	:	Disseminated Intravascular Coagulation.
DTIS	:	Direct Thrombin Inhibitors
DVT	:	Deep Vein Thrombosis
DWI	:	Diffusion-Weighted Imaging
ECG	:	Electrocardiography
Ecs	:	Endothelial Cells
EDRF	:	Endothelium-Derived Relaxing Factor
FDA	:	Food And Drug Association
FDP	:	Fibrin Degradation Products
GI	:	Gastrointestinal
FEIBA	:	Factor Eight Inhibitor By-Passing Activity
FFP	:	Fresh Frozen Plasma
HELLP	:	Hemolysis, Elevated Liver Enzymes, Low Platelets
HIT	:	Heparin-Induced Thrombocytopenia

List of Abbreviations (Cont.)

13-HODE	:	13-Hydroxy Octadecadienoic Acid
ICH	:	Intracerebral Hemorrhage
INR	:	International Normalized Ratio
ISTH	:	International Society Of Thrombosis And Haemostasis
IVC	:	Inferior Vena Cava
Ivig	:	Intravenous Immunoglobulin
JAAM	:	The Japanese Association For Acute Medicine
LA	:	Lupus Anticoagulant
LMWH	:	Low-Molecular Weight Heparin
LVEF	:	Left Ventricular Ejection Fraction
MCA	:	Middle Cerebral Artery
MERCI	:	Mechanical Embolus Removal in Cerebral Embolism
MI	:	Myocardial Infarction
MRV	:	Magnetic Resonance Venography
NPV	:	Negative Predictive Value
PAF	:	Platelet Activating Factor;
PAI	:	Plasminogen Activator Inhibitor
PAI-3	:	Plasminogen Activator Inhibitor-3
PTS	:	Post-Thrombotic Syndrome
PCC	:	Prothrombin Complex Concentrate
PCI	:	Percutaneous Coronary Intervention
PE	:	Pulmonary Embolism
PFA	:	Platelet Function Analyzer
PGE2	:	Prostaglandin
PGI2	:	Prostacyclin;
PRBC	:	Packed Red Blood Cells
PT	:	Prothrombin Time
PTT	:	Partial Thromboplastin Time

List of Abbreviations (Cont.)

rFVIIa	:	recombinant active Factor VII
rTM	:	Recombinant thrombomodulin
RV	:	Right Ventricular
SIRS	:	Systemic Inflammatory Response Syndrome
TAFI	:	Thrombin-Activatable Fibrinolysis Inhibitor
TEE	:	Transesophageal Echocardiography
TF	:	Tissue Factor
TFPI	:	Tissue Factor Pathway Inhibitor
t-PA	:	Tissue Plasminogen Activator
TRALI	:	Transfusion-Related Acute Lung Injury.
TTE	:	Transthoracic Echocardiography
UFH	:	Unfractionated Heparin
VKA	:	Vitamin K Antagonist
VTE	:	Venous Thromboembolism
vWD	:	Von Willebrand Disease
vWF	:	Von Willebrand Factor

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Introduction

Haemostasis is the system that enable the body to act in response to a haemostatic challenge. Not only does this system prevent blood loss from injured vessels, it also prevents the inappropriate cessation of flow ***(Rick et al., 2003).***

Haemostasis is regulated by 3 basic components, namely, the vascular wall, platelets, and the coagulation cascade. Normal hemostasis occurs as the result of a set of regulated processes to accomplish 2 functions; first, it maintains blood in a fluid, clot-free state, and second, it induces a rapid and localized hemostatic plug at the site of vascular injury ***(Riddel et al.,2007).***

Coagulation involves the regulated sequence of proteolytic activation of a series of zymogens to achieve appropriate and timely haemostasis in an injured vessel, in an environment that favours an anticoagulant state. In the non-pathological state, the inciting event involves exposure of circulating factor VII/VIIa to extravascularly expressed tissue factor, which brings into motion the series of steps which results in amplification of the initial stimulus, culminating in the conversion of fibrinogen to fibrin and clot formation. The precisely synchronized cascade of events is counter-balanced by a system of anticoagulant mechanisms, which serve to ensure that the haemostatic effect is regulated and does not extend inappropriately. Conversely, in pathological states, these events can escape normal control mechanisms, due to either inherited or acquired defects, which lead to thrombosis ***(Adams and Bird, 2009).***

Normal hemostasis requires an intact interrelating mechanism composed of vascular and tissue components, platelets, and coagulation proteins. Deficiency or disease of any of these components may cause either spontaneous or trauma-related hemorrhage. The intensive care setting, by

definition, involves a population that is characterized by multiorgan failure, polypharmacy, and multiple wounds of both accidental and iatrogenic variety. Such pathophysiology significantly stresses even an initially normal hemostatic mechanism ***(Rubin and Narra, 2010)***

Many critically ill patients develop hemostatic abnormalities, ranging from isolated thrombocytopenia or prolonged global clotting tests to complex defects, such as disseminated intravascular coagulation (DIC). There are many causes for a deranged coagulation in critically ill patients and each of these underlying disorders may require specific therapeutic or supportive management .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).***

Disorders of blood coagulation commonly occur in critically ill patients and become problematic in a variety of ways. Hemorrhage or thrombosis may be the dominant concern or may seriously complicate the management of other pathologic processes. Many of these disorders are complex and may quickly become life-threatening ***(Lachant, 2007).***

An adequate explanation for the cause of the coagulation abnormality is important, since many underlying disorders may require specific treatment. Treatment of coagulation abnormalities in critically ill patients should be directed at the underlying condition, but supportive therapy may be required. Deficiencies in platelets and coagulation factors in bleeding patients or patients at risk for bleeding can be achieved by transfusion of platelet concentrate or plasma products,

respectively. In addition, prohemostatic treatment may be beneficial in case of severe bleeding, whereas restoring physiological anticoagulant pathways may be helpful in patients with sepsis and DIC. A variety of altered coagulation parameters may be detectable, such as thrombocytopenia, prolonged global coagulation times, reduced levels of coagulation inhibitors, or high levels of fibrin split products ***(Levi et al.,2011).***

The coagulopathic conditions frequently encountered in the intensive care unit (ICU) can be arbitrarily divided into three categories: (i) those associated with serious bleeding or a high probability of bleeding, (ii) thrombotic syndromes or conditions associated with a higher probability of thrombosis, and (iii) systemic diseases associated with acquired selective coagulation factor deficiencies ***(Parker, 2009).***

Management of hemorrhage or thrombosis in critically ill patients requires weighing the answers to two questions: How threatening is the problem? and How dangerous is the treatment? ***(Parrillo and Dellinger ,2007).***

Aim of the Work

It discuss the incidence, types, etiology, clinical presentation, diagnosis and management of coagulation disorders that could occur or associate critically ill patient.

Physiology of Coagulation

The endothelial cell lining consists of the basement membrane and matrices of collagen and muscle fibres. This lining, in normal function, can be described as anti-thrombogenic, that is, it does not promote blood clotting. However, when damaged, it has the potential to release a number of substances that can be considered as pro-thrombogenic, that is, aimed at promoting blood clotting (table 1). The combination of these two potentials means that the endothelial cell lining can prevent thrombus formation during normal function but actively promote thrombus formation at times of insult and injury ***(Ranson, 2010).***

Table (1): Antithrombogenic and prothrombogenic potential of the endothelial cell lining

Antithrombogenic	***Prothrombogenic***
Protein S Thrombomodulin Heparan Heparan sulphate-proteoglycans Antithrombin and t-PA U-plasminogen activator Urokinase EDRF (NO), 13-HODE PGI2- PGE2	Tissue factor Von Willebrand factor PAI: 1 and-2 PAF Endothelins, Adhesion molecules Fibronectin Collagens Clotting factors V and VIII Factor IX receptor; factor X receptor

(Ranson, 2010).

PAI, plasminogen activator inhibitor; PAF, platelet activating factor; t-PA, tissue plasminogen activator; EDRF, endothelium-derived relaxing factor; 13-HODE, 13-hydroxy octadecadienoic acid; PGI2, prostacyclin; PGE2, prostaglandin.

A. Hemostasis:

Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms: (1) vascular constriction, (2) formation of a platelet plug, (3) formation of a blood clot as a

result of blood coagulation, and (4) eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently ***(Guyton and Hall, 2006).***

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; this instantaneously reduces the flow of blood from the ruptured blood vessel. 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).***

2) Platelet Plug:

Following endothelial injury, platelets adhere to the exposed subendothelial surface through platelet adhesion receptors, these platelet receptors bind von Willebrand factor and collagen, expressed on the subendothelial matrix. Adhesion triggers transmembrane signalling events that lead to platelet activation, and to activation of the platelet integrin (GP IIb-IIIa), which mediates platelet adhesion and aggregation at the injury site to form a platelet plug ***(Peck, 2007).***

When platelets come in contact with a damaged vascular surface, They begin to swell and become sticky so that they adhere to collagen in the tissues and to von Willebrand factor that leaks into the traumatized tissue from the plasma; they secrete large quantities of ADP; and their enzymes form thromboxane A2. The ADP and thromboxane in turn act on nearby platelets to activate them as well, and the stickiness of these additional platelets causes them to adhere to the original activated platelets. thus forming a platelet plug ***(Guyton and Hall, 2006).***