New Guidelines for Platelet Therapy in ICU

An Essay

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بسم الله الرحمن الرحيم
قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ
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Mohamed Ahmed Motawea

List of Contents

Subject *Page No.*

List of Abbreviations

Ab : Antibodies
ADAMTS13 : A Disintegrin And Metalloproteinase with Thrombospondin Motifs
ADP : Adenosine diphosphate
ADT : Adult therapeutic dose
APACHE : Acute Physiology and Chronic Health Evaluation
Aps : Apheresis platelets
aPTT : Activated partial thromboplastin time
ATP : Adenosine triphosphate
ATR : Allergic transfusion reactions
°C : The degree Celsius
Ca2+ : Calcium
CBC : Complete blood count
CCI : Corrected count increment
CFU : Colony-forming unit
CLEC-2 : C-type lectin receptor
DIC : Disseminated intravascular coagulation
DITP : Drug-Induced Thrombocytopenia
DNA : Deoxyribonucleic acid
DTI : Direct thrombin inhibitors
ELISA : The enzyme-linked immunosorbent assay
FcRγ : Fc receptor γ chain
FDP : Fibrin degradation products
FGF-4 : Fibroblast growth factor 4
Fl : Femtoliter
FNHTR : Febrile non-hemolytic transfusion reactions
GAS6 : The growth arrest–specific gene 6
GM-CSF : Granulocyte macrophage-colony, stimulating factor
GP : Glycoprotein
GPIbα : Glycoprotein Ibα

List of Abbreviations *(Cont...)*

GPVI : Glycoprotein VI
HBV : Hepatitis B Virus
HCV : Hepatitis C Virus
HELLP : Syndrome of haemolysis, elevated liver enzymes and low platelets
HIT : Heparin-induced thrombocytopenia
HIV : Human immunodeficiency virus
HLA : Human leukocyte antigen
HNA : Human Neutrophil Antigens
HPA : Human platelet antigen
HUS : Haemolytic uraemic syndrome
ICU : Intensive care unit
IgA : Immunoglobulin A
IL : Interleukin
INR : International normalized ratio
ISTH : The International Society on Thrombosis and Haemostasis
ITP : Idiopathic thrombocytopenic purpura
IVIG : Intravenous immunoglobulin
L : Liter
LDH : Lactate dehydrogenase
LDH : Lactate dehydrogenase
MAHA : Microangiopathic hemolytic anemia
MODS : Multiple Organ Dysfunction Scores
NAT : Nucleic acid amplification techniques
NO : Nitric oxide
OCS : Open canalicular system
PAR : Protease-activated receptors
PCs : Platelet concentrates
PCV : Packed cell volume
PDGF : Platelet-derived growth factor
PG : Prostaglandin

List of Abbreviations *(Cont...)*

PLCγ2 : Phospholipase Cγ2
PMPs : Platelet-derived Microparticles
PTP : Posttransfusion purpura
RNA : Ribonucleic acid
SAPS : Simplified Acute Physiology Scores
SDF : stromal cell derived factor
SH2 : Src homology 2
TM : Thrombotic microangiopathy
Tpo : Thrombopoietin
TRALI : Transfusion related acute lung injury
TTP : Thrombotic thrombocytopenic purpura
TXA2 : Thomboxane A2
VKAs : Vitamin K antagonists
VWF : von Willebrand factor

List of Tables

List of Figures

Introduction

Platelets are the second most abundant cells, after red blood cells, in the blood circulation. They are produced from their precursor megakaryocytes in the bone marrow. The major physiological role of platelets is to accumulate at sites of damaged blood vessel endothelium and initiate the blood clotting process. Platelet adhesion, activation, and subsequent aggregation at sites of vascular injury are critical to the normal arrest of bleeding ***(Li et al., 2012).***

Thrombocytopenia is a very frequent disorder in the intensive care unit. Many etiologies should be searched, and therapeutic approaches differ according to these different causes ***(Van der Linden et al., 2012).***

Thrombocytopenia presents a multifaceted pathogenic mechanism comprising hemodilution, increased platelet consumption, increased platelet destruction, decreased platelet production, increased platelet sequestration, and laboratory artifacts ***(MarcoSchulke et al., 2012).***

The many comorbidities in the severely ill patient make thrombocytopenia very common (40%) in intensive care unit patients. The risk of bleeding is high with severe thrombocytopenia and is enhanced in intensive care patients with mild or moderately low platelet counts when additional factors are present that interfere with normal hemostatic mechanisms (eg,

platelet function defects, hyperfibrinolysis, invasive procedures, or catheters). Even if not associated with bleeding, low platelet counts often influence patient management and may prompt physicians to withhold or delay necessary invasive interventions, reduce the intensity of anticoagulation, order prophylactic platelet transfusion, or change anticoagulants due to fear of heparin-induced thrombocytopenia. One approach to identify potential causes of thrombocytopenia that require specific interventions is to consider the dynamics of platelet count changes ***(Andreas et al., 2010).***

Platelet transfusions have greatly reduced the incidence of major haemorrhagic complications associated with the management of haematological and oncological disorders. The use of platelet transfusion continues to increase and platelets are an essential component in the management of selected patients with thrombocytopaenia. They need to be used judiciously as they are not free from risk. Platelet transfusions are not indicated in all causes of thrombocytopenia and maybe contra-indicated in certain conditions. Hence, the cause of thrombocytopenia should be established before making a decision about platelet transfusion ***(Paul et al., 2012)***.

Aim of the Work

To focus on different causes of platelet disorders in critically ill patients and decide whether or not to support the platelet count by platelet transfusion.

Chapter (1):
Pathophysiology of Platelet Disorders

Pathophysiology of platelet disorders

Physiology of platelets

1. Origin:

Platelets originate from the cytoplasm of bone marrow megakaryocytes. Platelets lack genomic DNA but contain megakaryocyte derived messenger RNA (mRNA) and the translational machinery needed for protein synthesis ***(Sharathkumar et al., 2008).***

Platelet production, or thrombopoiesis, is a complex process that can be schematically represented as consisting of four main steps. The first step is the production of the thrombopoietic stimulus, which drives the generation of megakaryocytes and ultimately platelets. Although a number of cytokines (ie, IL-3 [interleukin 3], IL-6 [interleukin 6], IL-11 [interleukin 11], GM-CSF [granulocyte macrophage-colony stimulating factor]) and chemokines (ie, SDF [stromal cell derived factor] and FGF-4 [fibroblast growth factor 4]) contribute to this process, thrombopoietin (Tpo) is widely recognized as the most potent known stimulator of platelet production ***(Kaushansky et al., 2008).***

Platelet production is tightly regulated by the hormone thrombopoietin (TPO), which is secreted by the liver at a constant rate (constitutive secretion) and acts on hematopoietic progenitor cells, bone marrow megakaryocytes, and platelets by binding to its receptor c-Mpl. Binding of TPO to c-Mpl leads to the differentiation of hematopoietic progenitor cells down the megakaryocyte lineage, maturation of megakaryocytes, and ultimately increased platelet production ***(Arnold et al., 2009).***

Once TPO is bound to c-Mpl, it is internalized, degraded, and removed from the circulation. Levels of free TPO are therefore controlled by the number of circulating platelets and the megakaryocyte mass, when platelet levels and mega-karyocyte numbers are low, free TPO levels are high and more platelets are produced; when platelet levels are high, circulating TPO levels are reduced ***(Arnold et al., 2011).***

2. Structure:

Circulating platelets are discoid in shape, with dimensions of approximately 2.0–4.0 by 0.5 μm, and a mean volume of 7–11 fl. Their shape and small size enables the platelets to be pushed to the edge of vessels, placing them in the optimum location to constantly survey the integrity of the vasculature. Platelets circulate in a concentration of 150,000-450,000 cells/mL. Of the total body platelets, about 70% stay in circulation while the remaining 30% are continually but transiently sequestered in the spleen. Platelets remain in circulation for an average of 10 days. Most platelets are

removed from the circulation by the spleen and liver after senescence, but a constant small fraction is continually removed through involvement in maintenance of vascular integrity ***(Sharathkumar et al., 2008).***

On peripheral blood smears stained with Wright-Giemsa stain, platelets appear as small, granular staining cells with a rough membrane, and are normally present as 3-10 platelets per high power oil-immersion field. Despite their simple appearance on the peripheral blood smear, platelets have a complex structure (Figure 1) Platelet internal structure has been divided into four zones:

- Peripheral zone
- Sol-gel zone
- Organelle zone
- Membrane zone ***(Sharathkumar et al., 2008).***

The **peripheral zone** includes the outer membranes and closely associated structures. The platelet has a surface connected system of channels called the open canalicular system (OCS). The walls of the OCS are included in this zone. The OCS provides access to the interior of the platelet to plasma substances, and an outlet channel for platelet products. The release of platelet products through the OCS after platelet activation is called "the release reaction" ***(Sharathkumar et al., 2008).***

The membranes of the platelet are rich in platelet receptors, which determine its specific cellular identity. These receptors are constitutively expressed on the platelets and