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Recent trends in Heparin induced thrombocytopenia in Intensive care units

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ
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List of Abbreviations

ACT	:	Activated clotting time
AF	:	Atrial fibrillation
APTT	:	Activated partial thromboplastin time
CAMP	:	Cyclic adenosine monophosphate
DVT	:	Deep venous thrombosis
ECT	:	Ecarin clotting time
ED	:	Emergency department
ELISA	:	Enzyme linked immune sorbant assay
FDA	:	Food and drug association
GP	:	Glyco protein
HIPA	:	Heparin induced platelet aggregation
H.I.T.	:	Heparin induced thrombocytopenia
ICU	:	Intensive care unit
IGg	:	Immunoglobulin
INR	:	international normalized ratio
I.V.	:	Intravenous
L.M.W.H	:	low molecular weight heparin
PCI	:	percutaneous coronary intervention
Pf4	:	platelet factor 4
SRA	:	serotonin release assay
UFH	:	unfractionated heparin
VKA	:	Vitamen k antagonist

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Introduction

Heparin is a glycosaminoglycan that is typically isolated from animal tissues and used pharmaceutically as an anticoagulant. The classic story of the discovery of heparin as told to generations of medical students has been that a second-year medical student working at Johns Hopkins University first isolated the material in 1916. This young man purified the anticoagulant from the canine liver; the Greek name for liver is *epar*—hence, the name "heparin." Although this story is historically accurate, the student did not isolate what we now call heparin; there are those who suggest that others should also be given credit for the discovery **(Warkentin TE and N engl,2009).**

In the late 1930s, workers in North America and Scandinavia pioneered the use of heparin as a treatment for thrombosis. In the 1970s, the first well-documented report appeared in the medical literature associating therapeutic heparin use with thrombocytopenia and thrombosis. Since that report, the association of thrombocytopenia and paradoxical thrombosis with the pharmaceutical use of the anticoagulant heparin has been a diagnostic conundrum for both clinicians and laboratorians alike **(Warkentin TE and N engl,2009).**

Since the introduction in 1937, heparin has now become the anticoagulant of choice for the prevention and treatment of venous and arterial

thromboembolism and several millions of units of heparin are used world wide**(Girolami B and Girolami A,*2006).***

Major indications for heparin are acute coronary syndrome, embolism from deep vein thrombosis or from atrial fibrillation, bypass surgery and valve replacement or repair**(Chong BH and *J Thromb,*2009).**

Heparin is a negatively charged mucopolysaccharide polymer named glycosoamino-glycan which is an anticoagulant released by mast cells and basophiles during the normal clotting process **(Thong CL and kamPCA,2005).**

Heparin is widely used for the treatment and prophylaxis of thromboembolic disease in medical and surgical patients**(Thong CL andkam PCA,2005).**

Heparin induced thrombocytopenia (HIT) is one of the most serious adverse events associated with the drug. HIT is an immune mediated prothrombotic complication that occurs with un-fractionated heparin and to lesser extent with low molecular weight heparin(LMWH)**(Greinacher A, EichlerP,2005).**

The fundamental paradox of HIT results from platelet-activating immune response triggered by the interaction of heparin with a specific platelet protein called protein factor 4(PF4)**(Selleng K et al.,2007).**

Heparin causes mild platelet aggregation in vivo especially in patients with activated platelets results in increased platelet sequestration in spleen & thrombocytopenia.Thrombocytopenia can be triggered via immune and non immune mechanism**(Thong CL, Kam PCA,2006).**

Clinically HIT can be differentiated to HIT type I, a benign non immune condition and HIT type II an immune mediated syndrome caused by antibody to the PF4/heparin complex**(Picker SM and Gathof BS,2004).**

Thrombocytopenia in HIT type I is usually mild and platelet counts rarely decrease below 100,000/dl Heparin administration should be continued & no specific therapy is required**(Greinacher A and Warkentin TE,2006).**

Immune mediated HIT is a disorder initiated by an immunological response to heparin exposure and characterized by an absolute or relative thrombocytopenia with paradoxically increased incidence of thrombosis and heparin should be discontinue**(Thong CL and Kam PCA,2005).**

Acute multiple strokes and pulmonary embolism has been detected in few cases of patients receiving heparin after prophylaxis of orthopedic

surgery. neuro-imaging has detect occlusion of the right common carotid artery**(Giossi A and del zotto,2012).**

The incidence of HIT varies from 0% in pregnant women receiving LMWH to 5% in patients undergoing orthopedic surgery receiving UFH**(Warkentin TE and Selleng K,2007).**

Despite the relatively high prevalence of anti-PF4/heparin antibodies in patients undergoing cardiac surgery, the incidence of HIT in this patient population is about 2.4%**(Warkentin TE and Selleng K,2007).**

The formation of anti-PF4/heparin antibodies varies from 2 to 5% in cardiology patients, from 15 to 30% in patients undergoing orthopedic surgery, and up to 30 to 70% in patients undergoing cardiac surgery**(Warkentin TE and N engl,2008).**

Several studies have assessed the frequency of HIT in ICU patients; the incidence of HIT in ICU patients is generally less than 2%**(Warkentin TEand N engl,2008).**

HIT is a clinicopathological syndrome with one or more clinical events (thrombocytopenia with or without thrombosis)**(Warkentin TE and Nengl,2008).**

In patients with HIT, thrombocytopenia typically occurs 5-10 days after initiation of heparin therapy (typical onset HIT) as the immune system requires several days to produce sufficient

amounts of anti-PF4/heparin anti-bodies**(Picker SM Gathof BS,2004).**

Some patients also develop acute respiratory or cardiac dysfunction, manifested as hypertension, tachycardia, angina pectoris, or dyspnoea. These manifestations may suggest pulmonary embolism because of the sudden pronounced platelet activation**(potzsch B and klovekornWP,2011).**

In some patients, HIT may occur after termination of heparin therapy. Thrombotic events or low platelet counts may draw attention to the presence of HIT. This 'delayed onset' HIT is associated with large numbers of anti-PF4/heparin antibodies, which lead to platelet activation in the absence of heparin**(Geinacher A and Warkentin TE,2006).**

Thrombocytopenia is a common laboratory abnormality in critically ill patients. Prospective data from 329 adult surgical ICU patients during one year showed that 41.3% had a platelet count less than 150,000/μl at some point. The most common etiology of thrombocytopenia in critical illness is sepsis (around 48%), although 25% of ICU patients have more than one cause**(Warkentin TE and N engl,2010).**

The most common thrombotic complications in patients with HIT include DVT (50%) and pulmonary embolism (25%). Other less common complications include myocardial infarction, cardiovascular accidents, arterial occlusive lower limb ischemia,

sinus vein thrombosis, mesenteric venous or arterial occlusion, and skin necrosis. Venous thrombosis is 4 to 10 times higher than arterial thrombosis**(potzsch B and klovekornWP,2011).**

The risk of bleeding in patients with HIT is relatively low, even at a platelet count of less than 20,000/μl. However, bleeding can occur due to platelet dysfunction, such as in patients with uremia**(S Gupta and MMGupta,2008).**

In a median of 8 days after the onset of heparin therapy, 10 to 20% of patients with HIT develop skin lesions in the form of erythematous nodules, subcutaneous plaques, or necrotic lesions**(Warkentin TE and Nengl,2008).**

If there is a clinical suspicion of HIT, all heparin should be stopped, including heparin used to 'flush' intravascular catheters, and regional use for dialysis and to coat catheters. In patients with strongly suspected or confirmed HIT who do not have active bleeding, prophylactic platelet transfusions are not indicated because this will lead to subsequent platelet activation and increased risk of thrombosis**(Giossi A et al.,2012).**

Pathogenesis of H.I.T.

Since the introduction in 1937, heparin has now become the anticoagulant of choice for the prevention and treatment of venous and arterial thrombo- embolism and several millions of units of heparin are used world wide**(Girolami B andGirolami A,*2006).***

Major indications for heparin are acute coronary syndrome, embolism from deep vein thrombosis embolism from atrial fibrillation(AF),by pass surgery and valve replacement of repair**(Chong BH and *J Thromb*, *Haemost*,2009).**

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Nonimmunemediated thrombocytopenia,also known as heparinassociated thrombocytopenia (HAT) and heparininduced

thrombocytopenia type I (HIT type I)**(Picker SM and Gathof BS,2004).**

Thrombocytopenia in HIT type I is usually mild and platelet counts rarely decrease below 100,000/dl Heparin intake should be continued & no specific therapy is required**(Geinacher Aand Warkentin TE,2006).**

Non-immune HIT, or HIT type I, is a self-limiting condition without any major complications that occurs in 10-30% of patients within 4 days after exposure to heparin. Heparin binds to PF4 with high affinity and inhibits adenylcyclase. This leads to a decrease in intra-cellular cyclic adenosine monophosphate (cAMP) levels with subsequent reduction in the platelet activation threshold and mild platelet aggregation and thrombocytopenia **(Picker SM and Gathof BS,2004).**

HIT type I may occur in patients with sepsis, burn injuries, and vascular diseases, probably due to platelet hyperreactivity in these conditions. Thrombocytopenia in HIT type I is usually mild and platelet

counts rarely decrease below 100,000/μ**(Battistelli S and Genovese A, 2010).**

Immune mediated HIT is a disorder initiated by an immunological response to heparin exposure and is characterized by an absolute or relative thrombocytopenia with paradoxically increased incidence of thrombosis and heparin should be discontinued immediately**(Thong CL and kamPCA,2005).**

The major antigen responsible for this syndrome is PF4, which is synthesized by megakaryocytes and stored in platelet α-granules. Upon platelet activation, PF4 is released and binds anionic glycosamino-glycans on cell surfaces. The main function of PF4 is to inhibit the formation of megakaryocytes and angiogenesis, as well as modulating the immune response. Considerable amounts of PF4 are released after trauma, inflammation, surgical trauma, and in neoplasm**(Amiral J andPeynaud-Debayle E,1996).**

In HIT type II, heparin infusion displaces PF4 and produces structural changes on it, leading to the formation of a PF4/heparin complex. This complex is recognized as a 'foreign'