Obstacles in the Diagnostics and Therapy of Heparin-Induced Thrombocytopenia

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SUMMARY
An immune-mediated, severe, acquired prothrombotic disorder, heparin-induced thrombocytopenia type II (HIT II) occurs in 0.5-5% of patients exposed to unfractionated heparin longer than 5-7 days. Arterial and venous thromboses are induced by HIT II in about 35-50% of patients. Typical death rate for HIT is about 29%, while 21% of HIT patients result in amputation of a limb. The trend towards the occurrence of HIT due to the administration of low molecular weight heparins (LMWH) taking ever conspicuous place in the standard venous thromboembolism (VTE) prophylaxis has been more frequently observed recently. It is considered that LMWH may cause HIT II in about 0.25-1%. The need for further modification of HIPA assays with LMWH has been imposed in the HIT laboratory diagnostics, heretofore overburdened with complexity. There are several constantly opposing problems arising in HIT laboratory diagnostics, one of which is that in a certain number of patients immunologic assays detect nonpathogenic antibodies (mainly IgM or IgA heparin-PF4 antibodies) while, on the other hand, the occurrence of HIT pathogenetically mediated by minor antigens (neutrophil-activating peptide 2 or interleukin 8) may be neglected in certain cases. The following factors play an important role in the interpretation of each laboratory HIT assays performed: 1. correlation with HIT clinical probability test, the best known of which is 4T'score, 2. the interpretation of the laboratory findings dependent on the time of the thrombocytopenia onset, as well as 3. the sensitivity and specificity of each test respectively. The HIT diagnostics in the presence of other comorbid states which may also induce thrombocytopenia, more precisely known as pseudo HIT (cancer, sepsis, disseminated intravascular coagulation, pulmonary embolism, antiphospholipid syndrome, etc), represents a specific clinical problem.
Keywords: heparin; induced; thrombocytopenia

INTRODUCTION

Heparin-induced thrombocytopenia type II (HIT II) is a severe, immune-mediated, acquired prothrombotic disorder, typically occurring in patients exposed to unfractionated heparin longer than 5-7 days. In about 35-70% of patients, HIT II induces arterial and venous thromboses. Death rate for HIT is about 29%, while 21% of HIT patients result in amputation of a limb [1-6].

The key 4T's score test characteristic of utmost importance is the presence of thrombocytopenia. Applying the improved definition for HIT (a drop in platelet counts of 50% or greater instead platelet counts below 150,000/cm^3), Warkentin found 8 times greater HIT incidence (4.8% vs. 0.6%) in the group of 665 patients exposed to heparin due to elective hip arthroplasty [2, 3, 7].

Regularly performed daily platelet count analyses, awareness of the significance of relative thrombocytopenia determination along with intense clinical follow-up contribute to establishing an early diagnosis and preventing the occurrence of potentially life-threatening complications [1-3, 8].

The HIT incidence depends not only on the criteria used for the detection of thrombocytopenia (absolute or relative thrombocytopenia), but also on the type of population receiving the heparin drug (surgical or non-surgical, i.e. medical patients), type of heparin received, as well as on the fact whether a patient has been previously exposed to heparin [1-9].

The trend towards the occurrence of HIT due to the administration of the low molecular weight heparins (LMWH), taking ever conspicuous place in the standard venous thromboembolism (VTE) prophylaxis, has been more frequently observed recently.

HIT occurs more frequently in surgical than in medical patients. HIT incidence in orthopaedic patients receiving subcutaneous prophylactic heparin is approximately 5% with unfractionated heparin (UFH) and 0.5% with LMWH, while it is approximately 0.7% in medical patients exposed to therapeutic porcine UFH and 0.8% given subcutaneous UFH. The incidence in medical patients given LMWH for prophylaxis or treatment has been found to be 0.8% [2, 10]. HIT risk is significantly increased in surgical patients receiving thromboprophylaxis with UFH than in those receiving it with LMWH (OR 13.93; 95% CI, 4.33-44.76) [11].

A study encompassing 1754 medical patients who received LMWH for prophylaxis or treatment of thrombosis (prevention and treatment of VTE, arterial fibrillation, coronary artery disease, cerebrovascular disease and other) indicates that HIT occurs more frequently during the first 2 weeks (0.80%, 95%

CI 0.43-1.34) in patients with prior exposure to UFH or LMWH (1.7%) than in those without prior exposure to heparin (0.3%) (OR=4.9; 95% CI 1.5-5.7) [9, 12]. Also, these data suggest that in those medical patients who develop immune HIT while receiving LMWH treatment the occurrence of arterial or venous thromboembolic complications is to be expected as often as in patients treated with UFH [9]. Certain randomized controlled trials suggest that the risk of thrombocytopenia and HIT in medical patients is similar to that in patients who receive either LMWH or UFH [7, 13]. On the other hand, this is in contrast with the findings determining an about 10-fold reduction in HIT with LMWH compared with UFH for thromboprophylaxis in surgical patients [14].

Compared with UFH, LMWH in the prevention of HIT may have greatest absolute benefit in females undergoing surgical thromboprophylaxis [11, 13].

Physicians should be cautious with patients to receive LMWH, when the same measures of HIT prevention and early detection are demanded as in patients exposed to UFH, especially in the first weeks of treatment [9].

LMWH is noted to generate H-PF4 antibodies less frequently while it generates IgA and IgM antibodies more frequently than IgG antibodies. According to some authors, this may account for a lower risk for clinical HIT with LMWH in comparison with UFH [7].

DIAGNOSIS OF HIT

A timely detection of skin changes may help a physician to establish an early diagnosis of HIT. This disease is specifically characterised by the presence of skin necrosis which is given the maximum number of points in the 4T's score, just like the occurrence of new thrombosis. Erythematous skin lesions receive equal intermediate points as detected progressive or recurrent thrombosis. Acute systemic reaction, equally to skin necrosis, is awarded the maximum points. Acute systemic reaction is manifested by several clinical symptoms and signs occurring 30 minutes after heparin intravenous bolus, such as fever or chills, tachycardia, hypertension, dyspnea, chest pain or tightness, flushing, cardiopulmonary arrest, nausea, vomiting, diarrhoea, transient amnesia and headache [14, 15].

The patients with skin changes have HIT-IgG antibodies but in some cases, thrombocytopenia can be only relative with a drop of ≥50% or, more rarely, even completely absent [14, 15].

The vivid illustration of the importance of the above statements represents the case of the patient with erythematous skin lesions at the sites of LMWH injection, who subsequently received an iv. bolus of UFH that resulted in acute systemic reaction.

In some of such patients, acute systemic reaction may be manifested by fatal cardiopulmonary arrest, thus endangering the patient's life [15].

Acute systemic reaction can be associated with abrupt decline in the platelet count resulting from heparin bolus and presumably reflects the biological consequences of sudden generalized platelet activation. Acute systemic reaction occurs in about 25% of HIT patients who receive an intravenous heparin bolus at a time when they form HIT antibodies [4, 14].

As opposed to typical HIT occurring between 5th and 10-14th day of ongoing heparin treatment, a rapid onset HIT occurs before the 5th day of ongoing repeated heparin therapy. A rapid platelet count drop (rapid onset HIT) occurs due to a prior exposure to heparin, typically up to 100 days, though the literature reports its occurrence even 165 days following the discontinuation of prior heparin therapy [16].

Delayed onset HIT can occur up to over 5 weeks (9-40 days) after withdrawn heparin [14, 17, 18]. Delayed onset HIT is characterized by high titres of IgG antibodies to heparin-PF4 [17]. The delayed onset HIT can occur in patients exposed to UFH alone or in combination with LMWH, sometimes even after hospital discharge. Patients with LMWH induced HIT have a longer delay in the onset of symptoms compared with patients with UFH-induced HIT [19].

More frequent detection of LMWH induced HIT has imposed the need for further modification of the complex HIT laboratory diagnostics, for instance heparin-induced platelet activation (HIPA) assays with LMWH. There are several constantly opposing problems arising in the HIT laboratory diagnostics. One is that in a certain number of patients immunologic assays detect nonpathogenic antibodies (mainly IgM or IgA heparin-PF4 antibodies) while, on the other hand, the occurrence of HIT pathogenetically mediated by minor antigens (neutrophil-activating peptide 2 or interleukin 8) may be neglected in certain cases.

IgG antibodies are generally stated to represent the main pathogenic substrate in the development of HIT II, while the role of antibodies to heparin-PF4, IgM class and IgA class remains controversial. In the opinion of some authors, IgM and IgA classes of antibodies may occur as a consequence of other diseases. Therefore, in clinical practice the use of tests which detect only IgG heparin-PF4 antibodies are recommended for diagnosis [20, 21, 22]. On the other hand, some authors draw attention to possible pathogenic importance of IgM and/or IgA antibodies [20, 21]. Antigenic heparin-PF4 assay is restricted by its inability to detect non-heparin-PF4 antigens, which is especially important for HIT II where antibodies specific for neutrophil-activating peptide 2 or interleukin 8 are generated [20].

It is claimed that it is not possible to confirm HIT II diagnosis by laboratory tests in up to 5%-10% of patients, even when up-to-date functional and antigenic assays, available in clinical practice, are used [23].

The following factors play an important role in the interpretation of each laboratory HIT assays performed: 1. the correlation with HIT clinical probability test, the best known of which is 4T'score; 2. the interpretation of laboratory findings dependent on the time of thrombocytopenia onset, as well as 3. the sensitivity and specificity of each test, respectively [1-6, 8].

The complexity of interpreting laboratory findings is indicated by the presence of crossreactive PF4/heparin antibodies in other autoimmune diseases like antiphospholipid syndrome [24].

The HIT diagnostics in the presence of other comorbid states which may also induce thrombocytopenia, more precisely known as pseudo HIT (cancer, sepsis, associated disseminated intravascular coagulation (DIC), pulmonary embolism, thrombolytic therapy administration, antiphospholipid syndrome, posttransfusion purpura, paroxysmal nocturnal haemoglobinuria), represents a specific clinical problem.

Pseudo-heparin-induced thrombocytopenia (pseudo-HIT) is defined as a clinical condition highly resembling HIT where the existence of HIT antibodies is excluded based on two sensitive assays, the functional and antigenic [8, 25, 26]. Since HIT parameters may be accompanied by negative or indeterminate HIT diagnostic assays, sometimes it may be hard to make a clear differential diagnosis between HIT and pseudo-HIT [8, 25, 26].

Also, it is important to point out the significance of the fact that thrombosis occur as the main manifestation of HIT II, while haemorrhage is the major manifestation of most other types of thrombocytopenia [1-5].

MANAGEMENT OF HIT

The introduction of new anticoagulants by a certain number of clinicians raised suspicion whether some anticoagulants, such as foundaparinux, play the role only in the prevention of HIT onset, regarding the fact that they still lack the official registration for HIT therapy as anticoagulant drugs. Efficient officially recognized nonheparin anticoagulants used in HIT therapy with proved clinical benefit are lepirudin, argatroban, danaparoid sodium and, in certain groups of patients, bivalirudin [1-5].

Though the literature states cases where HIT was successfully treated with fondaparinux, it also describes several cases of HIT occurring after fondaparinux administration [27-31]. One of them is a case of a 48-year-old female patient who underwent bilateral knee replacement without apparent preoperative or postoperative exposure to heparin. After 7-day prophylactic fondaparinux administration (2.5 mg sc), flank pain occurred due to bilateral adrenal infarction accompanied by a platelet fall to 39×10^9/L. The HIT diagnosis was confirmed with strongly positive serotonin releasing assay and positive immunologic test with heparin-PF4 antibodies. Fondaparinux was replaced with argatroban and later warfarin [27].

Fondaparinux is found to be associated with the formation of anti-PF4/heparin antibodies. Unlike LMWH, anti-PF4/heparin antibodies with fondaparinux have poorer reactivity, which suggests a very low risk of HIT with fondaparinux [2, 29].

New trials place special emphasis on the treatment of isolated HIT (HIT without thrombosis at the moment of diagnosis). Considering the data that isolated HIT is complicated with a new thrombosis developed in 30 days following the discontinuation of heparin in 52.8% and that a low-dose danaparoid proved to be insufficient, the full therapeutic dose of non-heparin anticoagulants danaparoid and lepirudin are recommended both in isolated HIT and HIT with thrombosis [1, 2, 4, 32].

Though improvements in early diagnosis of HIT and new treatment options succeeded in decreasing until recently a rather high both mortality rate in HIT and the percentage of patients surviving with major complications (e.g. limb loss, stroke) from 20% to 6% - 10%, this disease still represents a potentially serious and life- threatening condition [4].

It is little known how beneficial adjunctive therapeutic methods, such as plasmapheresis, antiplatelet drugs, intravenous immunoglobulins, may be in the therapeutic outcome in patients with heparin-induced thrombocytopenia and thrombosis (HITT). A study shows that late plasmapheresis performed 4 days after the onset of HIT II increases the mortality among the HITT patients, while other case reports demonstrate that late plasmapheresis is a useful, salvage method in HIT with thrombosis resistant to standard therapeutic regimen with danaparoid sodium and lepirudin [33].

Introduction of warfarin is not recommended in the acute stage of HIT before platelet count normalisation or, at least, upon a recovery of platelet count to over 100×10^9/L. This attitude is based on the fact that HIT is a consumptive process and may cause depletion of the natural anticoagulant protein C. Too early introduction of warfarin may exacerbate protein C depletion, which can disturb the balance between the natural anticoagulant and procoagulant proteins and lead to greater thrombotic risk, warfarin-induced thrombosis and venous limb gangrene [34, 35].

The first step in managing a patient with HIT is complete discontinuation of any form of heparin use (UFH or LMWH), primarily, heparin prescribed by a physician. Also, this implies total avoidance of sometimes neglected or overlooked exposure of a patient to heparin through the use of heparin flushes, heparin in dyalisate, continuous hemofiltration catheters, heparin-coated catheters, guidewires, and devices containing heparin [34].

Medical staff should be instructed to replace heparin used for flushing central and peripheral catheters with isotonic sodium chloride solution or nonheparinized solution. When a differential diagnosis of thrombocytopenia is considered, it must be kept in mind that the exposure to heparin is frequent in hospital and that the contact with and administration of heparin may not be registered in the patient's medical documentation [34].

CONCLUSION

Diagnostics and therapy of HIT patients demand great care, dexterity and cooperation of a multidisciplinary expert team of various profiles. The introduction of novel diagnostic methods and drugs in the prophylaxis and therapy of HIT is likely to contribute to more adequate treatment of this serious and potentially fatal disease.

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Замке при дијагностиковању и лечењу тромбоцитопеније изазване хепарином

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КРАТАК САДРЖАЈ

Тромбоцитопенија изазвана хепарином *II* (у нашој номенклатури „хепарином индукована тромбоцитопенија" – ХИТ *II*) је тешко, имунолошки посредовано, стечено тромбофилно стање које се јавља код 0,5-5% особа код којих је лечење нефракционисаним хепарином трајало дуже од 5-7 дана. Артеријске и венске тромбозе се јављају код 35-50% болесника са ХИТ *II*. Стопа смртности од овог обољења је 29%, док се ХИТ компликује ампутацијом екстремитета код 21% болесника. Услед све чешће примене нискомолекуларних хепарина у профилакси венског тромбоемболизма, уочен је тренд све чешће појаве ХИТ *II* изазване овим лековима. Сматра се да нискомолекуларни хепарини могу изазвати ХИТ код 0,25-0,8% особа лечених овом терапијом. У лабораторијској дијагностици ХИТ, која је веома сложена, намеће се потреба за модификацијом агрегацијских есеја с нискомолекуларним хепаринима. Постоји неколико проблема везаних за дијагностиковање ХИТ. Један од њих је да постоји одређен број болесника код којих се имунолошким есејима откривају непатогена антитела (углавном антитела хепарин-тромбоцитног фактора 4 *IgM* или *IgA* класе), док се, с друге стране, у неким случајевима занемарује појава ХИТ узрокованог тзв. минорним антигенима (неутрофилни активирајући пептид 2 или интерлеукин 8). Наведени фактори имају важну улогу у тумачењу сваког теста за постављање лабораторијске дијагнозе ХИТ: 1. корелација с тестом клиничке вероватноће, од којих је најпознатији 4Т бодовни систем; 2. интерпретација лабораторијског теста у односу на време настанка тромбоцитопеније; и 3. сензитивност и специфичност сваког теста посебно. Дијагностиковање ХИТ уз заступљеност других придружених стања која такође могу изазвати тромбоцитопенију (карциноми, сепса, дисеминована интраваскуларна коагулација, емболије плућа, антифосфолипидни синдром итд.) представља посебан клинички проблем.

Кључне речи: хепарин; индукована; тромбоцитопенија

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