CASE REPORT
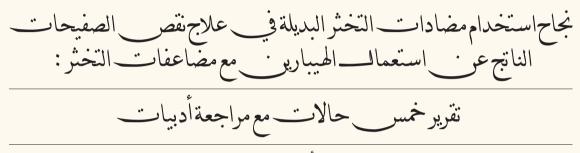
Successful Use of Alternative Anticoagulants in the Management of Heparin-induced Thrombocytopenia with Thrombotic Complications
Report of 5 cases and review of literature

*Salam Alkindi,[1] Owen P Smith,[2] Helen Enright[2]

نجاح استخدام مضادات التخثر البديلة في علاج نقص الصفيحات الناتج عن استعمال الهيبارين مع مضاعفات التخثر :

تقرير خمس حالات مع مراجعة أدبيات

سلام الكندي، أون سميث، هلن انرايت

الملخص: يُعد الهيبارين من أكثر الأدوية المضادة للتخثر استخداما لسهولة استعماله، لكن في الوقت نفسه يمكن أن يسبب مضاعفات قد تهدد حياة المريض، وإحدى هذه المضاعفات متلازمة نقص الصفيحات، التي تحصل في 3–5% من المرضى الذين يُعالجون بالهيبارين، وتكون مصاحبة للخُثار في 1% من الحالات. ندرج هنا تقريرا لخمس حالات أُصيبت بمتلازمة نقص الصفيحات الناتج عن استخدام الهيبارين تم علاجها بنجاح باستخدام مضادات التخثر البديلة: الدانابورويود والهيريودين. كان وَسِيط الوقت بين تناولهم للهيبارين وظهور أعراض المتلازمة (10.2) يوما (المدى بين 14 – 7 يوما). انخفض عدد الصفيحات إلى متوسط (ل/9^10 x 38.4) (ل/9^10 x 82–12). كان هناك دليلٍ على وجود خُثار عند المرضى الخمسة، وكان عند أربعة منهم دلائل سريرية وإشعاعية على انصمام رئوي، ومريض واحد ثبت إصابته بخُثارٌ وَرِيديَ عميق، كما أُصيب مريض آخر بنخر جلدي واسع النطاق في البطن والفخذين. كان فحص تكدّس الصفيحات إيجابيا عند مريضين، بينما كان غير حاسم عند مريض واحد، وسلبيا عند مريضين. أعطي مضاد التخثر داناباروريود لمريضين بينما عولج الثلاثة الآخرون بالهيريودين حتى عاد تعداد الصفيحات إلى الحد الطبيعي خلال فترة استغرقت بين 4 إلى 14 يوما (المتوسط 6 أيام) بعد تشخيص المتلازمة. كان المرضى في حالة خطيرة لكن لم تكن هناك وفيات. التوقف الفوري عن استخدام الهيبارين مهم للغاية، والبدء باستخدام مضادات التخثر البديلة يُعد ضروريا حين حصول تخثر.

مفتاح الكلمات: هببارين غير مُجزَّأ، هبارين قليل الوزن الجزيئي، نقص الصفيحات الناتج عن الهبارين، داناپورويود، هيريودين.

ABSTRACT: Heparin is one of the most frequently used anticoagulants. It is easy to use, but can be associated with life-threatening side effects. One of these is heparin-induced thrombocytopenia syndrome (HITS), which develops in about 3–5% of patients exposed to heparin and is associated with thrombosis in 1% of cases. We report here the successful treatment of five patients with HITS who were treated with alternative anticoagulants namely danaparoid or hirudin. The median time between their exposure to heparin and onset of symptoms and or signs was 10.2 days (range 7–14 days). Platelet counts decreased to a mean of 38.4×10^9 /l ($12–82 \times 10^9$/l). All five patients had evidence of thrombosis; four patients had clinical and radiological evidence of pulmonary emboli, one patient had confirmed deep vein thrombosis (DVT) and one patient had extensive skin necrosis of the thighs and abdomen. Platelet aggregation test were positive in two patients, inconclusive in one patient and negative in two patients. Two patients were anticoagulated with danaparoid and three with hirudin until their platelet counts returned to normal between 4 and 14 days (average 6 days) following the recognition of the syndrome. Our patients had significant morbidity, but no mortality. Immediate withdrawal of heparin is of paramount importance and introduction of alternative anticoagulant is necessary in the presence of thrombosis.

Keywords: Unfractionated heparin; Low-molecular weight heparin; Heparin-induced thrombocytopenia; Hirudin; Danaparoid; Case report; Oman

[1]*Department of Haematology, Sultan Qaboos University Hospital, Muscat, Oman; [2]Department of Haematology, The Adelaide & Meath Hospital, incorporating the National Children's Hospital, Tallaght, Dublin, Ireland.*
Corresponding Author email: sskindi@squ.edu.om

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Heparin is one of the most useful drugs in the prevention and treatment of arterial and venous thromboembolic diseases. It is generally very well tolerated, but it can be associated with a number of serious side effects, heparin-induced thrombocytopenia syndrome (HITS) being one of them.[1]

There are two types of HITS. Type 1 HITS is mild, transient, non-immune-mediated thrombocytopenia and occurs commonly following the institution of heparin. It is believed to be due to platelet aggregation and removal by the reticuloendothelial system. It is not associated with thrombosis, and no treatment is required; heparin withdrawal also may not be necessary. Type II, or immune-mediated HITS, on the other hand is a more serious condition. It is thought to be due to immunoglobulin (usually immunoglobulin G (IgG), but also IgM and IgA).[1] It usually develops 5–14 days following exposure to all types of heparin, including low molecular weight heparin (LMWH), or immediately following the second exposure to heparin.[2]

Heparin dependent antibodies are frequently encountered, however thrombocytopenia/thrombosis is seen only in about 3–5% of patients exposed to heparin, with thrombosis seen in about 1%. Usually this occurs 5–10 days after the initiation of heparin therapy.[3,4,5] The incidence of thrombocytopenia was thought to be lower in LMWH as compared to unfractionated heparin (UFH); however, recent data suggest it is not as low as was initially thought.[6] This may be due to the lesser interaction between LMWH and platelet PF4,

which is crucial for the development of HITS.[3-5] We report here five cases of Type II HITS developed following exposure to heparin sodium salts including LMWH. Our aim is to highlight the need for vigilance in monitoring patients with recent exposure to heparin preparations, allowing early recognition of the syndrome and commencement of prompt and appropriate therapy.

Methods

The medical records of our patients who were diagnosed as having HITS over a one year period were retrospectively evaluated. Once the diagnosis of HITS is suspected, samples are taken for aggregation studies. Platelet aggregation is performed by combining platelet-poor patient serum to donor platelets, and adding heparin, or a control solution of normal saline. Platelet aggregations are then measured for 15 minutes using a platelets aggregometer, and the test is considered positive when light transmission changes ≥20%.

Case One

A 55 year-old man was admitted for total hip replacement and received LMWH (enoxaparin) prophylaxis. A week later he became breathless, weak, and fainted with sudden onset of apnoea; the electrocardiogram (ECG) monitor showed slow atrial fibrillation. Cardiopulmonary resuscitation was performed, after which emergency angiography showed bilateral pulmonary emboli. Preoperative

Table 1: Summary of important demographic and haematological parameters of all five cases

Case #	1	2	3	4	5
Age (years)	55	68	42	51	74
Sex	M	F	F	M	M
Platelets at admission x 10⁹/l	201	182	225	182	139
White blood count at admissions x 10⁹/l	7.1	12.9	7.2	6.1	7.8
Type of heparin used	Enoxaparin	Enoxaparin	Minihep	Minihep	Minihep
Duration of heparin therapy (days)	9	14	11	14	7
Nadir platelets counts x 10⁹/l	78	48	12	25	35
Therapy used	Danaparoid	Danaparoid	Hirudin	Hirudin	Hirudin
Day 10 platelet count x 10⁹/l	240	287	261	210	156
Time to normal counts (days)	9	7	4	6	9

Table 2: Therapeutic agents used to treat heparin-induced thrombocytopenia (HIT)

Agent	Dose	Grade of recommendation	Advantages	Disadvantages
Danaparoid sodium	2000–3000 loading done 150–200/hr maintenance dose	1B	Can be used in severe renal failure. Used in HIT prophylaxis in high risk patients.	Monitoring only by anti-Xa 5–10% cross reactivity with heparin
Hirudin (lepirudin)	0.4 mg/kg bolus 0.15 mg/kg/hr continuous infusion	1C	Easily monitored by activated partial thromboplastin time (APTT)	Contraindicated in renal failure, allergic reactions
Fondaparinux	2.5–5 mg	2C	Effect could be reversed by activated factor VII	Requires anti-Xa for monitoring,

counts showed Hb 14.1 g/dl, white blood cells (WBC) 7.1 x 10^9/l, platelets 201 x 10^9/l. At the onset of the pulmonary embolism, the blood counts showed Hb 10g/dl, WBC 20 x 10^9/l and platelets 82 x 10^9/l. His platelet count dropped further to 78 x 10^9/l. Further investigation showed prothrombin time (PT) 10.6 seconds, activated partial thromboplastin time (APTT) 26.1 seconds, fibrinogen 2.36 g/l, D-dimers > 6.4 < 12.8. Testing for HIT by aggregation studies was negative. Treatment was commenced with danaparoid infusion, while the tissue plasminogen activator (t-PA) and LMWH were discontinued. He developed transient acute renal failure requiring dialysis due to transient hypotension. The platelet count returned to normal on day nine following the episode, when danaparoid was discontinued and he was commenced on warfarin.

Case Two

A 68 year-old diabetic woman with ischaemic heart disease and peripheral vascular disease was admitted with bilateral gangrenous toes [Figure 1]. She was treated with heparin followed by aortoiliac stenting. Postoperatively she received clexane (enoxaparin) subcutaneous injections. Two weeks later, she became acutely dyspnoeic with tachycardia, melena, and multiple necrotic skin lesions developed at the site of heparin injections on her thighs and abdomen [Figure 1]. Investigations showed Hb 6.3 g/dl, WBC 12.9 x 10^9/l, platelets 48 x 10^9/l. HIT testing by platelet aggregometry was equivocal. The LMWH was discontinued. She was treated with red cell and platelet transfusion, and her anticoagulant treatment was changed to danaparoid (organon) 750 IU twice a day (BD) subcutaneously (SC) until

her platelet count returned to normal; this occurred 7 days following the initiation of danaparoid.

Case Three

A 42 year-old woman with menorrhagia underwent a total abdominal hysterectomy. Prophylaxis with "minihep" (low dose unfractionated sodium-heparin: 5000 IU BD SC) was commenced the day before surgery. On admission the complete blood count (CBC) was as follows: Hb 10.9 g/dl, WBC 7.2 x 10^9/l and platelets 225 x 10^9/l. She was on minihep post-operatively until she was discharged. Three days after the discharge, she presented with vaginal bleeding and right calf pain and tenderness. A Doppler scan confirmed deep vein thrombosis. Full blood counts showed Hb 10.8 g/dl WBC 5.3 x 10^9/l, platelets 12 x 10^9/l; the coagulation screen was normal apart from elevated D-dimers. She was transfused with platelets. HIT testing by platelet aggregometer was negative. She was treated with hirudin until her platelet count returned to normal (on the fourth day of hirudin infusion), and was subsequently anticoagulated with warfarin for 6 months.

Case Four

A 51 year-old man underwent anterior resection at another hospital for a colon carcinoma. He received unfractionated heparin (UFH, minihep) prophylaxis pre- and postoperatively. His CBC prior to surgery showed Hb 10.7 g/dl, WBC 6.1 x 10^9/l, platelets 182 x 10^9/l. Three weeks later, he was admitted to our hospital with a 3-day history of gradual onset of dyspnoea and haemoptysis with swelling of

Figure 1: Case Two **(A)** Multiple necrotic thigh lesions at site of heparin injection; **(B - F)** Bilateral gangreneous toes.

both calves. The ventilation perfusion scan was indicative of pulmonary emboli. His blood count now showed Hb 11.2 g/dl, WBC 6.1 x 10⁹, platelets 49 x 10⁹/l. The platelets decreased further to 25 x 10⁹/l during the next few hours. The coagulation screen was normal apart from elevated D-dimers. HIT testing using aggregation studies was positive. He was commenced on hirudin and his platelet count returned to normal on the sixth day when hirudin was stopped. He was anticoagulated with warfarin for a further 6 months.

Case Five

A 74 year-old man was admitted for repair of an abdominal aortic aneurysm. His past medical history included hypertension, polycythaemia rubra vera and reflux oesophagitis. His counts prior to operation showed Hb 16.1 g/dl, WBC 7.8 x 10⁹/l, and platelets 139 x 10⁹/l. He received UFH (minihep) prophylaxis pre- and postoperatively. One week postoperatively he became breathless and wheezy. A repeat blood count showed Hb 12.4 g/dl, WBC 8.1 x 10⁹/l, platelets 74 x 10⁹/l, partial pressure of oxygen (pO_2) 10.3, partial pressure of carbon dioxide (pCO_2) 5.0, and phosphate buffered saline (pH) 7.43. Oxygen saturation was 92%. PT 12.4 seconds, APTT 27.9 seconds, D-dimers >1.0 <2.0. During the next 24 hours, his platelet count decreased further to 35 x 10⁹/l and HIT testing was positive. A ventilation perfusion scan was indicative of multiple pulmonary emboli. He was anticoagulated with hirudin until his platelet count

recovered to normal nine days later. He was then anticoagulated with warfarin.

Discussion

HIT is an antibody mediated reaction caused by exposure to heparin leading to devastating thrombotic complications.[7,8] Following the administration of heparin, it binds to platelet factor 4 (PF4) triggering a humoral response and the formation of anti-platelet antibodies; these are generally IgG, although IgM and IgA antibodies have been reported.[2,3,9] Evidence for the pathogenic role of platelet antibodies is strengthened by the typical onset of the syndrome after 5–15 days of heparin treatment. *In vitro*, the addition of serum from patients with HITS leads to platelet aggregation and platelet secretory response. This is the basis for the enzyme-linked immunosorbent assay (ELISA) test used in the diagnosis of HITS. PF4 released by the (α granules) of the platelets appears to be crucial in heparin induced platelet activation and binding to IgG.[10,11]

THROMBOSIS & HEPARIN

Heparin–PF4 complex binding to IgG leads to platelet aggregation and thrombocytopenia. The thrombosis, however, is thought to be due to platelet microparticles. Negatively charged heparin binds tightly to the positively charged protein tetramer PF4 leading to platelet activation and release of microparticles that are highly procoagulants, setting off the coagulation cascade

with further platelet activation/release.[11,12] This leads to activation of thrombin and generation of a hypercoagulable state. Acute inflammatory endothelial injury (seen in some surgical patients in particular), in connection with heparin associated IgG, may increase the generation of tissue factor leading to the activation of an intrinsic coagulation pathway. These two processes lead to thrombin activation/generation.[12-16] Incidentally, our five patients had a recent surgical intervention prior to the development of this syndrome although medical patients can also develop this complication. This has led authorities in the field to suggest a double "HIT" is needed with simultaneous antigen exposure and proinflammatory signal in order to trigger a strong immune response.[17]

CLINICAL FEATURES

HITS should be suspected when the platelet count drops by 50% or more from the initial count prior to heparin therapy, although the absolute count may not drop below 150×10^9/l. However, the development of thrombosis, which can be either arterial or venous, cannot be predicted from the level of the platelet count.[14,15] Thrombosis can occur at any site, but lower limbs, cardiac and central nervous systems are the most common sites resulting in limb gangrene, myocardial infarction or stroke. Other manifestations include skin necrosis in particular at the site of a subcutaneous heparin injection as seen in one of our patients. Haemorrhage and disseminated intravascular coagulations are rare, but recognised clinical features. Significantly all our patients showed evidence of thrombosis including DVT and pulmonary emboli; in one of them it was significant enough to cause a haemodynamic instability that could have resulted in death. Two of our patients showed evidence of bleeding and one of them developed skin necrosis [Figure 1]. It is interesting to note that one of our cases also had background of polycythaemia, a condition that is known to predispose to thrombosis. There have been similar previous reports of HITS with polycythaemia.[18]

DIAGNOSIS OF THE CONDITION

When HITS is suspected, measures should be taken to confirm the diagnosis before major complications develop and to exclude other causes of thrombocytopenia. The most important aspect of the diagnosis is the clinical suspicion and demonstration of a drop of >50% in platelet level prior to the episode, even if the platelet level is still within the normal range. Warkentin has suggested the Warkentin's "4Ts" pretest clinical scoring system which helps stratify patients into low, moderate and high pretest probability of HIT. It is based on the level of *T*hrombocytopenia, *T*iming of thrombocytopenia in relation to heparin exposure, *T*hrombosis and presence of another diagnosis to explain the *T*hrombocytopenia.[19]

There are two major diagnostic pathways: activation assays which measure platelet activation and include the platelets aggregation test (PAT), and serotonin release test (SRT). PAT is the most widely used laboratory screening test. It is based on the demonstration of platelet aggregation upon mixing patient serum with normal donor platelets in the presence of heparin. Although the test is specific, its sensitivity is only about 50%. The sensitivity could be improved by a) using the same sample of heparin which was used to treat the patient; b) using normal washed platelets, and c) screening the controls for arginine[13,1] expressions as opposed to histidine which result in altered affinity in platelets Fc gamma RIIA.[11,20] The SRT, on the other hand, is based on exposure of normal donor platelets to radioactive[14] C-serotonin and mixing it with recently heat inactivated patient serum and heparin. Platelet activation leads to increased release of serotonin and radioactivity. The limitation of this test is the need to use a radioactive substance, which a lot of laboratories try to avoid. Also, it requires time and the result may not be available quickly enough for a clinical decision; however, it has a sensitivity of 90% and a specificity approaching 100%. Flow cytometry is a promising alternative which avoids radioactivity, but it has not yet been widely adopted or evaluated for routine clinical testing.[21-23] The antigen detection assay or ELISA based assay is used to assess the presence of antibodies against heparin/PF4 complex. This test is gaining popularity, though it is associated with about 3–20% false positive results in the absence of thrombocytopenia or thrombosis. False negative results can occur particularly when antibodies against other than heparin/PF4 complex do exist;[24] however, in general, it has an excellent negative predictive value.

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MANAGAMENT

The mainstay of the management of HITS is that all forms of heparin, including LMWH should be stopped. Efforts should be made to establish the diagnosis and/or to exclude other causes of thrombocytopenia. Treatment is required for the original thrombotic process for which heparin was given, and for the treatment of the complications that follow the onset of HITS. There may be a case for prophylactic anticoagulation as over 50% of patients with isolated HITS subsequently develop thrombosis.

ALTERNATIVE ANTICOAGULANTS

There are two alternative anticoagulants danaparoid and hirudin. Danaparoid is composed of low molecular weight heparanoid comprising heparin sulphate (84%), dermatan sulphate (12%) and chondroitin sulphate (4%). It is different from heparin and LMWH in the degree of sulphation and molecular weight.[4,20, 21,25] It is useful in thrombosis associated with heparin (both in arterial and venous types) and in coronary heart disease and haemodialysis. However, it is associated with a number of disadvantages particularly, 5–10% cross reactivity with heparin, bleeding with no available antidote, long half-life and it has no effect on thrombin. It also requires anti-Xa assay for its monitoring. The dose is not well established, however 2000 IU intravenous or SC as a bolus dose followed by 2000 IU twice daily is recommended for patients of average build. It is available in Europe, but not in the USA.

Hirudin is a leech-derived direct thrombin inhibitor peptide achieving an effective anticoagulation in HITS and without cross-reactivity with heparin. Hirudin and other anti-thrombins such as hiruko and argatroban have the advantage of easy monitoring of anticoagulant effects using APTT. It is given at a dose of 0.4 mg/kg bolus followed by 0.15 mg/kg/hour continuous infusion and adjusted according to the desired APTT. It is metabolised by the kidneys thus it is not recommended in patients with renal failure, or in patients undergoing haemodialysis.

Ancord is a potent defibrinogenating agent derived from the Malayan pit viper. It converts fibrinogen into abnormal non-crosslinked fibrin polymers that are cleaved rapidly and removed from the circulation. It is used in pulmonary thromboembolic disease, deep vein thrombosis and thrombosis complicating HITS. It is administered at a dose of 1 u/Kg by intravenous route and monitored using fibrinogen levels; however, it lacks any activity against thrombin which is increased in many patients with HITS. It also has an unpredictable effect on fibrinogen and does not achieve its anticoagulants effect rapidly.[26]

Fondaparinux (Arixtra) is composed of a modified pentasaccharide similar to heparin. Its selectively inhibits Xa and it was shown to be effective in HIT. Fondaparinux does not bind to PF4 and as such does not seem to cause HIT itself, although there have been some recent reports of HIT antibodies present without causing platelets depletion or thrombosis. Its effects could be theoretically reversed by recombinant activated factor VII.[27]

Warfarin is a useful oral agent, particularly when further anticoagulation is required; however, warfarin is not recommended until 5 days have elapsed from the onset of HITS, or the platelet counts have returned to normal. The use of warfarin early on in the acute phase can cause a precipitant drop in protein C levels causing further thrombosis; however, if the patient is already anticoagulated with warfarin, it may be continued.[26]

Other alternative treatments, including anti-platelet agents such as aspirin, dipyridamole and dextran, have being used particularly to inhibit platelet aggregation and further platelet activation; however, they have no role in inhibiting thrombin activity and as such they are not routinely recommended. Plasmapheresis has also been suggested to remove the circulating abnormal IgG. Plateletpheresis has also been employed particularly to stop platelet destruction in a cardiopulmonary bypass situation. Intravenous immunoglobulin has also been used to treat HITS with some anecdotal success. Prophylactic platelet transfusions should be restricted to patients with active bleeding as giving platelets in this condition may worsen thrombosis.

Conclusion

Heparin, although commonly used for management of thromboembolic disease, can be associated with very serious side effects including thrombocytopenia and thrombosis. HITS is frequently unrecognised until the development

of a serious life or limb threatening thrombotic episode so platelets counts should be monitored regularly in patients receiving heparin. These cases demonstrate that HITS can occur with the use of all forms of heparin including prophylactic, low dose UFH and LMWH. Our data suggest that HITS is also seen with sodium heparin salts as opposed to calcium salts as reported previously. The use of an aggregation test is useful guide, but it is associated with a number of false negative results and the diagnosis has to remain a clinical one. Serological based testing is gaining momentum and its one of the most useful tests available. Prompt withdrawal of all forms of heparin including heparin flushes, or heparin impregnated intravascular catheters, is crucial to avoid further complications. Early introduction of alternative anticoagulation therapy is recommended when thrombosis is present, or the risk of developing thrombosis is high. Prompt recognition of this syndrome, discontinuation of all forms of heparin and institution of alternative anticoagulant therapy are the cornerstones of the successful management of this condition.

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