

# MASSIVE PULMONARY EMBOLISM FOLLOWING HEPARIN-INDUCED THROMBOCYTOPENIA

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**SUMMARY** – Immunomediated heparin-induced thrombocytopenia still presents a serious problem, especially when accompanied by thromboembolic complications. We report on a rare case of massive pulmonary embolism following perioperative prophylaxis with unfractionated and low-molecular-weight heparin. The lack of efficacious and safe heparin substitution only allowed for immediate heparin discontinuation and application of adjuvant therapy. A few days after heparin cessation the platelet count tended to return to normal, leading to the patient's full recovery and discharge from the hospital. Heparin therapy requires careful examination of previous history of heparin use as well as close platelet monitoring for up to three weeks of therapy cessation.

**Key words:** *Pulmonary embolism – chemically induced; Thrombocytopenia – chemically induced; Anticoagulants – adverse effects; Heparin – adverse effects*

## Introduction

Heparin-induced thrombocytopenia (HIT) is defined as a platelet count decrease that occurs shortly after the initiation of heparin therapy. Platelet count tends to return to normal upon cessation of heparin therapy and has no other apparent cause. Heparin-induced thrombocytopenia type II (HIT II) is an immunoglobulin-mediated, drug induced side effect of heparin therapy<sup>1</sup>. It is the result of the generation of an autoantibody (most often IgG, rarely IgA or IgM) to a complex of unfractionated heparin with the anti-heparin protein platelet factor 4 (PF-4). Heparin-PF-4 antibody complexes can bind to the platelet Fc receptor and cause platelet activation, agglutination and arterial thrombosis<sup>2</sup>. According to literature data, the incidence of HIT varies markedly depending on the clinical setting and type of heparin used. Up to three per cent of the patients receiving unfractionated heparin will develop HIT II with occasionally severe thromboembolic complications, which are difficult to treat<sup>3</sup>. Unlike type II, type I HIT is not immunomediated, the platelet count remains above  $80 \times 10^9/L$ , and

usually no complications occur<sup>4</sup>. It appears to be caused by a direct agglutinating effect of heparin on the platelets.

## Case Report

A 75-year-old woman was admitted to surgery department because of a left hip fracture. Results of preoperative routine laboratory tests were within the normal values, including platelet count ( $238 \times 10^9/L$ ), prothrombin time, fibrinogen and partial thromboplastin time. Thromboprophylaxis with unfractionated subcutaneous heparin ( $3 \times 2500$  IU/24 h) was started on admission, continued for seven days, and was then replaced by low-molecular heparin (heparin sodium, s.c. 3000 U/day). Osteosynthesis was performed on day 5 of hospitalization, followed by rapid and successful recovery. However, on day 10, the patient suddenly developed tachypnea, tachycardia and hypotension. Blood gas analysis and ECG were compatible with pulmonary embolism, and the patient was transferred to the intensive care unit. Chest x-ray revealed no significant findings, however, ventilation/perfusion scan showed evidence of massive pulmonary embolism with severe hypoperfusion of the whole right lung. Routine laboratory tests were repeated including a wide coagulation profile (prothrombin time, thrombin time, partial thromboplastin time, fibrinogen, soluble fibrin monomers, antithrombin III, protein C, protein S). All param-

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ters showed normal values, with the exception of platelet count, which was extremely low ( $8 \times 10^9/L$ ). Factor V Leiden, factor II mutation and MTHFR mutation measured two days later were negative. Doppler ultrasonography of the major deep veins of both legs showed no signs of thrombosis. HIT and consecutive pulmonary embolism by a “white clot” were suspected. HIT was confirmed by ID-Heparin/PF4 antibody test. The main problem was the substitution of heparin with an alternative anticoagulant such as lepirudin, danaparoid sodium or argatroban, none of which have been registered or available for use in Croatia. Therapy consisted of aspirin  $2 \times 500$  mg/day and high doses of human IgG. Six days later the platelet count was  $114 \times 10^9/L$ , and in the next five days it rose to  $203 \times 10^9/L$ . Except for the hip fracture and osteosynthesis, no other risk factor for thrombosis was determined. Under these circumstances, further anticoagulant therapy was found unnecessary, and the patient was discharged. No complications were observed over the next twelve months of follow-up.

## Discussion

There are several problems regarding the diagnosis and treatment of HIT. As many diseases are known to be associated with thrombocytopenia, a diagnostic score or an algorithm was required to support the suspicion. However, only HIT II, HIT-thrombosis, HIT-thrombosis syndrome, or immunomediated HIT had a real clinical relevance because of possible thromboembolic incidents.

The question of genetic predisposition to HIT has been dealt with by several authors. It has been found that the His<sub>131</sub>/Arg<sub>131</sub> polymorphism at amino acid 131 of the human FcγIIa receptor (the only Fcγ receptor found on human platelets) may act as a predisposing factor<sup>5,6</sup>.

It is also well known that unfractionated heparin (UFH) carries a much greater risk of inducing HIT than low-molecular-weight heparin (LMWH). The incidence of HIT caused by UFH may be as high as ten per cent depending on the type and dose regimen, whereas that of the LMWH-induced HIT is less than one per cent<sup>7</sup>. It seems that bovine heparin is more likely to cause HIT than porcine heparin, but not all authors share this opinion<sup>8</sup>. The role of the patient population type has also been recognized<sup>9</sup>. For example, cardiac surgical patients are at a greater risk of developing heparin-induced antibodies when treated with UFH than the orthopedic ones. Surprisingly, however, orthopedic patients are more likely to develop HIT. Generally, HIT is less common in medical than in surgical patients.

There is no doubt that a previous heparin exposure may predispose a patient to HIT upon re-exposure. This includes the already “forgotten” treatment with local heparin preparations or small doses of heparin to prevent venous line thrombosis.

Only a small number of patients with HIT-IgG will develop thrombocytopenia<sup>10</sup>. Thrombotic events occur almost exclusively in patients who have developed HIT antibodies and thrombocytopenia, rather than in patients who have developed only antibodies.

For an early and prompt recognition of HIT a simple procedure should be followed. Daily platelet monitoring is needed if the patient receives a full dose of UFH, and every other day if an intermediate dose is administered<sup>7</sup>. When the treatment involves low doses or LMWH, twice-a-week administration is usually sufficient. For uncertain reasons, many HIT-IgG patients do not become thrombocytopenic.

Three different forms of HIT have been identified, two of which occur early and one which is delayed<sup>11</sup>. Acute-onset thrombocytopenia appears immediately after exposure in about 15 per cent of patients but abates if therapy is continued. This form is probably due to the non-immunomediated platelet-clumping effect of heparin. The second form presents with a mild platelet count reduction (usually no less than  $100^9/L$ ) and develops 2-4 days after heparin initiation. The platelet count tends to return to normal within the next five days regardless of whether heparin administration continues or not. These two forms are not associated with thromboembolic incidents. The third form usually appears between days 4 and 15 after heparin administration and the platelet count is typically decreased to less than  $100^9/L$ , or reduced by more than 50 per cent. This form is immunomediated and associated with the binding of immunoglobulin to the platelets in the presence of heparin, resulting in platelet aggregation. Severe arterial and venous thromboembolism may develop or, less frequently, hemorrhagic complications may occur.

A delayed onset of HIT should be suspected when patients present with thrombocytopenia and thrombosis up until three weeks after heparin exposure. This syndrome could be caused by high titers of the platelet-activating IgG induced by heparin<sup>12</sup>.

Two main classes of laboratory assays have been developed to detect HIT antibodies: activation assays and antigen assays<sup>13</sup>. Of the various activation assays available, those using washed platelets and <sup>14</sup>C-serotonin release assay (SRA) or heparin-induced platelet activation are most accurate. Antigen assays, now commercially available, which are based on detecting antibodies against PF4 bound to hep-

arin or polyvinylsulfonate, respond to clinically insignificant antibodies more often than activation assays. However, several studies indicate that the results obtained by SRA and heparin-PF4 ELISA are generally in agreement in patients with the clinical diagnosis of HIT<sup>14</sup>.

There being no definite therapy for HIT, approaches to its treatment are varied and have produced mixed success<sup>15</sup>. Therefore, it is important first to know what not to do. Patients with HIT should not be given warfarin, which may induce a precipitous fall in the protein C level. Depletion of protein C leads to microvascular thrombosis caused by imbalance between procoagulant and anticoagulant factors. An increase in thrombin generation enhances the risk of catastrophic thromboembolic events such as warfarin-induced venous limb gangrene. Any kind of heparin administration should be ceased immediately, including LMWH which, *in vitro*, shows a cross-reactivity of up to 90 per cent<sup>1</sup>.

Hirudin, a 65-amino acid polypeptide originally isolated from the salivary glands of the medicinal leech, has been successfully used in the treatment of arterial and venous thrombotic complications produced by HIT<sup>16</sup>.

Danaparoid is a heparinoid compound related to LMWH<sup>15</sup>. Heparin-associated antiplatelet antibodies exhibit cross-reactivity to danaparoid in approximately 10-20 per cent of patients.

Lepirudin is a hirudin derivative that does not exhibit cross-reactivity when used for treating thromboembolic disorders in pregnancy<sup>13</sup>. It should be given until the platelet count is recovered. The efficacy of therapeutic doses of danaparoid or lepirudin in preventing death, amputation, or new thromboembolic complications in HIT patients does not differ largely, but the risk of bleeding seems to be higher in lepirudin-treated patients<sup>17</sup>. Lepirudin is a safe anticoagulant in hemodialysis patients but close monitoring is required because of its renal clearance<sup>18</sup>. The half-life of lepirudin, normally 1.3 hours, is prolonged up to 30 times in hemodialysis patients, with a terminal half-life approaching two days. Another important factor that precludes the use of lepirudin is its high cost, which may exceed the cost of hemodialysis.

Argatroban, a direct thrombin inhibitor, is a small synthetic molecule that binds reversibly and specifically to the catalytic domain of thrombin. Argatroban is hepatically metabolized but not renally cleared, and drug-specific antibodies have not been known to develop.

A study by Lewis *et al.* demonstrated that argatroban treatment produced significant benefits in clinical outcome and disease progression in HIT patients in comparison with control subjects<sup>19</sup>. Specifically, argatroban significantly re-

duced the risk of death caused by thrombosis as well as that of new thrombosis. The argatroban-treated patients showed a more rapid recovery of the platelet count. These benefits were realized without increasing the bleeding risk in patients as compared to control subjects.

Numerous other drugs are used to produce an anticoagulant effect, but only a few of those mentioned above have been approved for HIT treatment.

The antiplatelet agents such as aspirin and dextran may raise the platelet count in some HIT patients, but their poor efficacy (against the potent agonist HIT-IgG) and serious hemodynamic side effects limit their use as adjunctive therapy agents<sup>15</sup>. A high dose of IgG administered i.v. can displace antiheparin antibodies (HIT-IgG) from the platelets, but its use must be considered in terms of adjunctive therapy. Finally, plasmapheresis has been used in HIT patients to help remove the immune complexes that cause the disease.

Anecro is a defibrinogenating snake venom, which has been used to treat HIT<sup>20</sup>. However, it may not be an ideal agent for this purpose. In HIT patients treated with anecro thrombin generation is not reduced and may even increase.

Successful application of thrombolysis in the treatment of massive pulmonary embolism or arterial thrombosis secondary to HIT has also been described in several case reports<sup>21-23</sup>. Only small doses of the thrombolytic agent have been applied locally, and all patients are reported to have been in life-threatening condition.

An anecdotal report of pulmonary embolectomy after coronary artery bypass grafting due to heparin-induced thrombocytopenia has also been published<sup>24</sup>.

Basic recommendations for the treatment of thrombosis in HIT are as follows:

- Discontinue all heparin including heparinized line flushes and catheters.
- Avoid platelet transfusions since they can contribute to the formation or extension of a thrombus.
- Do not use LMWH.
- Do not use coumadin (warfarin) alone.
- Hirudin (lepirudin/Refludan) – drug approved by the Food and Drug Administration (FDA) for the treatment of thrombosis in HIT: 0.4 mg/kg bolus, then 0.15 mg/kg/h to keep PTT 1.5-2.5 x mean of normal. Reduce dose in renal failure. Hirudin is NOT yet FDA-approved for use in DVT prophylaxis.
- Danaparoid (Orgaran) is NOT approved by the FDA for intravenous administration. However, the usual dosage is 2500 U i.v. bolus, then 400 U/h during 4 h, then 300 U/h for the next 4 h, and finally 150-200 U/h, adjust to

keep anti-Xa 0.5-0.8 U/ml. Reduce dose in renal failure. Follow platelet count when using danaparoid and discontinue the drug if thrombocytopenia persists or worsens. Danaparoid is FDA-approved for DVT prophylaxis.

- Treat patients with hirudin OR danaparoid while initiating warfarin until INR is at least 2.

It should be pointed out that none of the heparin substitutes mentioned above has been registered or approved for use in Croatia, and adjuvant therapy alone will not be sufficient in most cases.

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## Sažetak

## MASIVNA PLUĆNA EMBOLIJA NAKON TROMBOCITOPENIJE IZAZVANE HEPARINOM

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Imuna trombocitopenija izazvana heparinom još uvijek predstavlja ozbiljan problem, osobito ako je praćena tromboemboličnim komplikacijama. Ovdje prikazujemo rijedak slučaj masivne plućne embolije nastale nakon profilaktične primjene nefrakcioniranog i niskomolekularnog heparina. Manjak učinkovitog i sigurnog nadomjestka za heparin ostavio je samo mogućnost neposrednog ukidanja heparina i uvođenja pomoćne terapije. Nekoliko dana nakon prestanka liječenja heparinom broj trombocita počeo se normalizirati, a nakon toga bolesnica se je potpuno oporavila i bila otpuštena iz bolnice. Liječenje heparinom zahtijeva brižno prikupljanje anamnestičnih podataka o ranijoj primjeni ovoga pripravka te pažljivo praćenje broja trombocita i do tri tjedna nakon prekida heparinske terapije.

Ključne riječi: *Plućna embolija – kemijski izazvana; Trombocitopenija – kemijski izazvana; Antikoagulansi – štetni učinci; Heparin – štetni učinci*