

Review Article

Some New Perspectives in Heparin-Induced Thrombocytopenia Type II

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PATHOMECHANISM AND DIAGNOSIS

Heparin-induced thrombocytopenia type II (HIT II), is a serious complication, which especially, in cardiac surgery is associated with a high morbidity and mortality (1). In patients with HIT II, antibodies against heparin bonded to platelet proteins, mostly platelet factor 4 (PF-4), are generated, which leads to the formation of antigen–antibody complexes. These immune complexes bind to platelets and stimulate platelet aggregation and thrombin generation. Clinically, this sequel imposes a rapid decrease of the platelet count and often is associated with such thromboembolic complications as venous thromboses, pulmonary embolism, stroke, or myocardial, mesenteric or peripheral infarction (2–4).

The reported incidence of HIT II varies largely from 1–20% (2–4), which may be attributed to the use of different laboratory tests and clinical criteria for confirmation of the diagnosis. However, widely accepted clinical criteria for HIT II are a rapid decrease of the platelet count, within 7 to 4 days after the first application of heparins or within hours to days after re-exposure, mostly below 100,000/ μ L, and/or thromboembolic events despite adequate anticoagulation, as, for example, monitored by a prolonged activated thromboplastin time (APTT), during heparinization.

The “golden laboratory standard test” for HIT II is the C_{14} -labeled serotonin release assay (C_{14} SRA), a functional test in which the release of serotonin as a marker of platelet activation is observed in the presence of heparin and HIT II antibodies. However, because this assay re-

quires time-consuming pre-analytical procedures and involves radioactive material, it is mostly restricted to research use in specialized laboratories. The heparin-induced platelet activation assay (HIPAA) is another functional test that evaluates platelet agglutination in the presence of heparin and HIT II antibodies and has gained increasing importance as a routine functional test for HIT II (5). However, because the agglutination is qualified by the physician, the interpretation of the test is influenced by the investigator (6). Recently, a modification of the C_{14} SRA has been introduced that measures the serotonin release in an enzyme-linked immunosorbent assay (ELISA) (EIA-SRA) (7), which revealed a good correlation to the results of the C_{14} SRA. Further studies must prove how extensively this test can be integrated into routine diagnostics.

Apart from functional assays, heparin-PF-4 antibodies (HPF-4/AB) can be directly evaluated by ELISA techniques. However, despite the fact that these tests are time consuming and expensive, it seems that, especially in patients undergoing cardiac surgery, the test results are not specific, because 20–60% of patients have been evaluated as HPF-4/AB positive without any clinical evidence of HIT II (8–11). Furthermore, two additional aspects seem to limit the value of these tests. First, because only HPF-4/AB antibodies are detected, other antibodies sometimes responsible for HIT II are not excluded (12). Second, in contrast to functional tests, a cross reactivity of low molecular weight heparins or heparinoids cannot be evaluated: However, recently a quick (20 min) and inexpensive (approximately \$10 US) particle gel immunoassay for evaluation of HPF-4/AB (ID-HPF4) has been introduced (13). Furthermore, investigations must elucidate to what degree this test improves conventional ELISA techniques. However, because of its low costs and speed, it may serve as a screening assay for HIT II.

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TREATMENT

If HIT II is diagnosed or suspected, the application of heparin must be stopped, and an alternative anticoagulation must be instituted. Low molecular weight heparins and, in particular, the heparinoid danaparoid sodium have been used for this purpose. However, although these glycosaminoglycans reveal a weak potential for stimulating the development of HIT II antibodies, they are associated with a high cross reactivity of 90% (LMWH) and 10% (Orgaran™) if HIT II antibodies are present (14). In contrast, the recently introduced recombinant hirudin (r-hirudin), a direct thrombin inhibitor, is a protein that is not associated with such a risk. Recombinant hirudin has been successfully used (SC, IV) for low-dose thrombosis prophylaxis and for high-dose anticoagulation; for example, during dialysis or CPB in patients with HIT II (15). In addition, recent investigations suggest that r-hirudin, particularly in combination with the platelet glycoprotein IIb/IIIa antagonists, is an effective therapy in cases of acute HIT II (16).

However, despite the progress in the diagnosis and treatment of HIT II, if the platelet count decreases, and HIT II is suspected, thromboembolism often has occurred. Therefore, particular care must be taken in the prophylaxis of this disease by the reduction of the immunization. This, however, may best be achieved by the avoidance of unfractionated heparins (UFH) whenever possible and the use of alternative anticoagulants, such as LMWH, heparinoids (Orgaran™), and particularly such proteins as r-hirudin.

CARDIOPULMONARY BYPASS IN PATIENTS WITH HIT II

Anticoagulation during CPB seems to be the only field that poses a problem in patients diagnosed for HIT II. This must be attributed to the fact that, on the one hand, high-dose anticoagulation is necessary to avoid CPB thrombosis, and, on the other hand, the large wound area after thoracotomy/sternotomy needs immediate restoration of coagulation to avoid hemorrhage. Therefore, safe management of CPB requires a fast-acting anticoagulant, reliable point-of-care (POC) monitoring of the anticoagulant or its effect, and an immediate restoration of coagulation via biological/extracorporeal elimination or an antidote. However, to date, only anticoagulation using UFH monitored by the ACT or Hepcon HMS™ and its reversal via protamine fulfill these criteria.

One study recently proposed to delay surgery until the HIT II antibodies became undetectable in specific laboratory assays and to then perform anticoagulation during CPB with UFH (17). In these patients, after the short period of "contamination" with UFH during CPB, HIT II

antibodies remained untraceable. However, this study involved only 10 patients and lacks details regarding the duration of CPB. In addition, in cardiovascular patients, often the operation cannot be delayed for a period of approximately 40 days until the antibodies are cleared (18). Therefore, this strategy is only applicable for selected patients, and an alternative anticoagulation must be performed.

Orgaran™ has been used in large series of patients with HIT II for anticoagulation during CPB (19). Nevertheless, in addition to the discussed cross reactivity with HIT antibodies, the long elimination half-life of 15–20 hours and the unavailability of an antidote and reliable POC monitoring assay are relevant drawbacks of this agent. An improved regimen for Orgaran™ during CPB suggests a loading dose of 125 U/kg for the patient and 3 U/mL for the priming solution, followed by a continuous infusion of 7 U/kg/h up to 45 min before the conclusion of CPB (20). However, thromboses of the CPB as well as postoperative hemorrhage using this agent have been described (17). Preliminary *in vitro* studies suggest that POC monitoring of the anti-Xa activity of Orgaran™ which should be in the range of 1.5 IU/mL is possible and might contribute to a reduction of these complications (21). Moreover, extracorporeal elimination, as for example, via hemodiafiltration, to date has not been assessed adequately and needs further investigations. However, if this drug is used in patients with HIT II, the exclusion of cross reactivity with HIT II antibodies is a must.

With the introduction of r-hirudin the relevant drawbacks of Orgaran™ are avoided. As discussed previously, there is no cross reactivity with HIT II antibodies due to the protein structure. The rapid renal elimination (biological half-life of 1–2 h) and on-line monitoring via the ecarin clotting time (ECT) (22–24) enables tight control of the drug. The protocol was based on a bolus of 0.25 mg/kg for the patient and 0.2 mg/kg for the priming volume. The desired concentration of 3–4 µg/mL r-hirudin was maintained via repetitive boluses or a continuous infusion. After CPB, forced diuresis was initiated. Larger series of CPB procedures in patients with HIT II and nonimpaired function of the kidneys have been described, which were not associated with thrombosis of the CPB and increased bleeding (25). However, in the case of renal failure, because of the dramatically prolonged elimination half-life of about 100 hours, a persistent anticoagulant effect involves severe hemorrhage (25). Recent *in vitro* investigations suggest a potent elimination of r-hirudin via modified ultrafiltration using special hemofilters or plasmapheresis filters (26). Further *in vivo* studies must prove the clinical effectiveness of these procedures.

The combination of UFH with a potent inhibitor of platelet aggregation is another alternative strategy. The basic idea behind this concept is to use the established

features of UFH, such as monitoring of anticoagulation via the ACT and reversal by protamine, while inhibiting the HIT II reaction. Prostaglandins have been widely used for this purpose (27). Recently, Mertzluft et al. elaborated the protocol by monitoring the antiplatelet effect of epoprostenol via the Hemostatus II (Medtronic, Minneapolis, MN, USA) platelet function test and the immediate post-operative initiation of a r-hirudin infusion (28). This immediate potent thrombosis prophylaxis with r-hirudin seems to be a particularly important feature. With the cessation of the prostaglandin effect and recovery of platelet function, the patient may be at an increased risk for developing HIT II-associated complications because of circulating antigen/antibody complexes. However, the strong hypotensive effect of prostaglandins, which necessitate the titration of the drug, and the relative long running time of the platelet assay are time consuming and seem to be a limiting factor of this strategy. Therefore, we have modified this strategy by using the short-acting platelet glycoprotein (GP) IIb/IIIa antagonist tirofiban (Aggrastat, MSD) as the antiplatelet agent. These agents provide an effective inhibition of the HIT II-induced platelet aggregation (29–31), and the effect of fixed dosage protocols has been validated in large clinical trials in intervention cardiology (32, 33). The tirofiban dosage followed the RESTORE scheme; that is, a bolus of 10 $\mu\text{g}/\text{kg}$ 10 min before the application of 300 IU of UFH and a continuous infusion of 0.1 $\mu\text{g}/\text{kg}$ until 1 hour before conclusion of CPB. Anticoagulation during CPB was monitored via the ACT with a target value of 480 sec. The necessary dose of protamine after CPB was calculated with the Hepcon HMS (Medtronic, Minneapolis, MN, USA) after immediate re-infusion of the complete CPB volume. Immediately after arrival on the ICU, a continuous infusion of r-hirudin to an APTT of 40–60 sec was started. In a series of 25 patients with HIT II, in whom anticoagulation with r-hirudin during CPB was regarded as unsafe because of impaired renal function, this comprehensible protocol has been used without intra- or post-operative thromboembolic complications or post-operative hemorrhage. However, further investigations are necessary for a thorough validation of this strategy.

SUMMARY

We conclude that HIT II is a serious complication, particularly in patients undergoing cardiovascular surgery that involves CPB. New tests might contribute to the earlier diagnosis of this disease. However, the reduction of immunization by the use of alternative anticoagulants whenever possible seems to be the most effective strategy for the reduction of HIT II-associated complications.

If HIT II is diagnosed, r-hirudin is effective as an acute therapy (especially in combination with GP IIb/IIIa in-

hibitors) and also for further anticoagulation. If patients must undergo CPB, all current alternative anticoagulation concepts are associated with relevant drawbacks that put the patient at an increased risk for post-operative bleeding and/or CPB thrombosis. Currently, r-hirudin is most probably the best option for this purpose. However, when there is impaired renal function, the persistent anticoagulant effect is associated with hemorrhage. Further studies must evaluate whether extracorporeal elimination procedures, such as hemofiltration or plasmapheresis, are effective in avoiding such complications. Otherwise, the combination of UFH with a potent antiplatelet agent, especially with short-acting GP IIb/IIIa antagonists, is an attractive alternative.

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