

Heparin induced thrombocytopenia thrombosis (HIT/T) syndrome: diagnosis and treatment

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Abstract

Heparin induced thrombocytopenia thrombosis (HIT/T) is associated with a high morbidity and mortality. Diagnosis is essentially clinical and negative results of laboratory assays do not exclude the diagnosis. Treatment involves stopping all heparin immediately and giving an alternative thrombin inhibitor. The adoption of low molecular weight heparins is one reason for the reduced incidence of this disease in recent years.

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Heparin induced thrombocytopenia (HIT) is defined as a decrease in platelet count shortly after starting heparin, which resolves after stopping heparin and has no other apparent cause. Mild thrombocytopenia occurring within four days of starting heparin is the result of a direct effect of heparin on platelets. It is not immune mediated but appears to be caused by a direct agglutinating effect of heparin on platelets. It is not associated with thrombosis and resolves despite the continuation of treatment. Severe thrombocytopenia, usually occurring between four and 14 days after starting heparin, is associated with both arterial and venous thrombosis (HIT/T) and appears to be immune mediated. Immune HIT/T should be considered whenever the platelet count falls by 50% in a patient receiving heparin. Although typically associated with intravenous infusion of unfractionated heparin, immune HIT/T has been reported in association with subcutaneous low dose heparin, heparin flushes, heparin coated catheters, low molecular weight heparins, and heparinoids.¹ Thrombosis caused by the HIT/T syndrome often occurs at the same site as the thrombosis for which heparin treatment is being given, most commonly this is venous thromboembolism. Thrombosis is arterial in about 20% of cases and this can cause acute limb ischaemia, myocardial infarction, or stroke. With early recognition and intervention, mortality can be reduced from > 30% to < 10%.² The incidence of thrombocytopenia with prophylactic heparin treatment is about 4%, but the incidence of thrombocytopenia < 100 × 10⁹/litre is only about 0.2% and the risk of thrombosis is even lower.³ Similarly, the incidence of thrombocytopenia with therapeutic doses of heparin is in the order of 5%, although the risk of thrombocytopenia less than 100 × 10⁹/litre is higher, and the risk of thrombosis may be as high as 0.3–0.4%, about one in 300 patients.³ There

has been an apparent decline in the incidence of immune HIT/T in recent years, possibly as a result of: (1) the replacement of bovine with porcine derived heparin; (2) the shorter duration of heparin treatment; (3) the use of low molecular weight heparins; and (4) awareness of the condition, with monitoring of the platelet count and withdrawal of heparin when thrombocytopenia occurs.

In 1973, it was shown that both sera and purified IgG from two patients with HIT induced the aggregation of normal platelets in the presence of therapeutic concentrations of heparin.⁴ Since then, the platelet aggregating factor in HIT sera has repeatedly been shown to be IgG. Thrombosis is thought to occur by Fc receptor mediated platelet activation.⁵ Current evidence supports a mechanism by which the antibody binds to platelet membrane associated heparin platelet factor 4 (PF4) to form an immune complex, which binds to FcγRIIA receptors on the platelet membrane and on endothelial cells.^{6,7} This antibody receptor interaction initiates signal transduction and cell activation. Other platelet activating factors appear to have a synergistic effect and are probably important determinants for the development of HIT/T.⁸ Platelet activation caused by HIT antibodies results in the translocation of anionic phospholipids from the internal to the external leaflet of the platelet membrane.⁹ In the presence of an anionic phospholipid surface and tissue factor VIIa the tenase and prothrombinase complexes are assembled and the thrombin explosion is initiated. This might explain why HIT/T occurs more often in sick patients who have considerable tissue damage, and hence tissue factor exposure, either as a result of surgery, sepsis, or previous thrombosis. It is also possible that heparin dependent antibodies directly stimulate tissue factor exposure on endothelial cells.¹⁰ The thrombocytopenia can be caused by reticuloendothelial clearance of activated or antibody coated platelets. Paradoxically, thrombosis may be more likely in patients with reduced clearance of immune complexes and hence prolonged activation of endothelial cells and platelets.¹¹

Diagnosis

The diagnosis of immune HIT/T should be considered in any patient who develops a 50% reduction of platelet count while on heparin treatment. It is recommended that the platelet count is measured twice weekly in the first week or two of heparin treatment to detect the development of HIT early and thus prevent thrombosis.⁵ In addition, the diagnosis should be considered and the platelet count measured

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when a patient receiving heparin develops resistance to heparin or a new thrombosis while on treatment.

Laboratory tests can be used to support the diagnosis of immune HIT. However, the negative predictive value of these tests is generally < 50%, so that a negative result does not exclude the diagnosis. Therefore, the diagnosis of HIT should be made simply on the basis of a 50% reduction of platelet count in a patient receiving heparin for which there is no obvious cause. Laboratory tests can be useful when there are several potential causes of thrombocytopenia, but if there is a strong suspicion of HIT, stopping heparin should not be delayed while awaiting the results of laboratory tests.

Functional assays such as the platelet aggregation test (PAT) and serotonin release assay (SRA) give a high rate of false negative results.¹² These assays require fresh donor platelets and not all platelets are reactive to HIT sera. The reason for the variable platelet responsiveness is not yet explained. It is not simply a reflection of platelet Fc γ R2 receptor density or genotype.¹³ The sensitivity of the PAT is only about 30%.¹⁴ The test should be performed at high and low heparin concentrations to optimise specificity, the so called two point test.¹⁵ The heparin induced platelet activation assay (HIPA) is performed in a microtitre plate and has similar sensitivity to the PAT.¹⁶ The SRA is generally regarded as more sensitive than the PAT. This might be because washed platelets are used in the SRA and the washing process might partially activate them. This is supported by the observation that prestimulation of platelets with a low concentration of ADP has been shown to increase the sensitivity of the PAT.¹⁷ Recently, several flow cytometric techniques have been described for the detection of heparin dependent antibodies in samples from patients with immune HIT.^{18, 19} A potential advantage of this development is the ability to distinguish antibodies capable of causing immune HIT/T from uncomplicated HIT.²⁰ Further studies are required to determine inter-laboratory performance and the negative and positive predictive values and prognostic relevance of flow cytometric assays.²¹

Non-functional antibody detection assays are much more sensitive but have low specificity. Negative enzyme linked immunosorbent assay (ELISA) results have been obtained in patients with clinically apparent HIT and a positive SRA result.^{12, 22} Positive results have been found in up to 2% of normal controls, 4% of pregnant women, and 8% of disease controls not exposed to heparin for more than six months.¹² Furthermore, 50% or more of patients exposed to heparin without the development of HIT/T develop detectable antibodies by ELISA.^{22, 23}

Treatment

If there is a strong suspicion of immune HIT/T all heparin should be stopped, including heparin line flushes. An alternative thrombin inhibitor should be started. Although the platelet count might rise rapidly after stopping heparin there is still a risk of thrombosis for

several days. Oral anticoagulant treatment alone does not prevent thrombosis.²⁴ Low molecular weight heparins should not be used unless antibody crossreactivity is excluded.^{25, 26}

Danaparoid is a mixture of heparan sulphate, dermatan sulphate, and chondroitin sulphates. Less than 10% of heparin dependent antibodies crossreact with danaparoid and thrombocytopenia might resolve during danaparoid treatment even when crossreactivity is present.²⁷ Danaparoid is therefore a useful substitute for heparin, particularly in patients with a previous history of HIT/T who require anti-thrombotic prophylaxis. It has been used in patients with active HIT/T, either by continuous intravenous infusion or subcutaneous injection. Treatment can be monitored by anti-Xa activity and this is recommended in patients with renal impairment and in patients over 90 kg. The activated partial thromboplastin time (APTT) is not sensitive to the antithrombotic effect of danaparoid and therefore cannot be used for monitoring or dose adjustment. For simplicity, a standardised treatment regimen based on weight has been developed. Danaparoid has a long half life of plasma anti-Xa activity of approximately 24 hours. This should be considered when interrupting treatment for surgery or other invasive procedures and when overlapping treatment with oral anticoagulant treatment. Danaparoid is not neutralised by protamine sulphate. Platelet counts recover during treatment in approximately 90% of patients and mortality is reduced to 10%.²⁸

Thrombin inhibitors chemically unrelated to heparin are now available. Heparin dependent antibodies have no crossreactivity with these agents. Recombinant hirudin (Lepirudin) is a direct thrombin inhibitor. In a prospective multicentre study, 82 patients received one of four intravenous regimens. The incidence of the combined end point of death, amputation, or new thromboembolism was significantly reduced in patients treated with Lepirudin (25.4%) compared with historical controls (52.1%). Mortality was 8.6% in Lepirudin treated patients and 22.3% in historical controls. A sustained recovery of platelet count was seen in approximately 90% of patients. Bleeding rates were similar in both groups.²⁹ The APTT should be used to monitor treatment, aiming for an APTT ratio of 2.5, depending on the APTT reagent (product information should be consulted for dosing and details of laboratory monitoring). Renal impairment results in delayed clearance of Lepirudin.

Argatroban is a new synthetic thrombin inhibitor that was evaluated in a multicentre trial comparing treatment in 160 patients with HIT and 144 with HIT/T with a group of historical controls treated in different ways. Argatroban reduced the number of thromboembolic complications and related deaths, with no increased risk of major bleeding. Mortality was 18% in argatroban treated patients and 32% in controls. The limb amputation rate was

7% in patients treated with argatroban compared with 18% in controls and new thrombotic events were 30% and 11%, respectively.³⁰ The APTT can be used to monitor treatment. At the present time argatroban is not licensed in the UK.

Despite the use of potent thrombin inhibitors morbidity and mortality as a result of HITT is still high. Combination treatment with potent platelet inhibitors might improve outcome further and adequate clinical evidence is awaited.³¹

Conclusion

Although immune HIT/T is uncommon, when it does occur it is associated with a high morbidity and mortality. To reduce the risk of this syndrome low molecular weight heparins or heparinoids can be used in preference to unfractionated heparin. Frequent monitoring of the platelet count might permit the recognition of HIT/T and withdrawal of heparin treatment before thrombotic complications occur. The mechanisms responsible for HIT/T are not defined. A combination of platelet activation in the presence of heparin dependent antibodies appears to be necessary. The diagnosis of immune HIT/T is essentially clinical and negative results of laboratory assays do not exclude the diagnosis. If there is a strong clinical suspicion all heparin must be stopped immediately and an alternative thrombin inhibitor should be given. Both Lepirudin and danaparoid are licensed in the UK for the treatment of HIT/T. Advantages of Lepirudin are the complete absence of crossreactivity with heparin dependent antibodies and the ability to monitor treatment with the APTT. The development of heparin mimetics that do not lead to the formation of heparin PF4 dependent antibodies could potentially abolish the risk of immune HIT/T.³²

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