= Heparin @-@ induced thrombocytopenia =

Heparin @-@ induced thrombocytopenia (HIT) is the development of thrombocytopenia (a low platelet count) , due to the administration of various forms of heparin , an anticoagulant . HIT predisposes to thrombosis , the abnormal formation of blood clots inside a blood vessel , and when thrombosis is identified the condition is called heparin @-@ induced thrombocytopenia and thrombosis (HITT) . HIT is caused by the formation of abnormal antibodies that activate platelets . If someone receiving heparin develops new or worsening thrombosis , or if the platelet count falls , HIT can be confirmed with specific blood tests .

The treatment of HIT requires both protection from thrombosis and choice of an agent that will not reduce the platelet count further . Several alternatives are available for this purpose and mainly used are danaparoid , fondaparinux , argatroban and bivalirudin

While heparin was discovered in the 1930s , HIT was not reported until the 1960s .

= = Signs and symptoms = =

Heparin may be used for both prevention and the treatment of thrombosis . It exists in two main forms : an " unfractionated " form that can be injected under the skin or through an intravenous infusion , and a " low molecular weight " form that is generally given subcutaneously (administered under the skin) . Commonly used low molecular weight heparins are enoxaparin , dalteparin , nadroparin and tinzaparin .

In HIT , the platelet count in the blood falls below the normal range , a condition called thrombocytopenia . However , it is generally not low enough to lead to an increased risk of bleeding . Most people with HIT will therefore not experience any symptoms . Typically the platelet count will fall 5 ? 14 days after heparin is first given ; if someone has received heparin in the previous three months , the fall in platelet count may occur sooner , sometimes within a day .

The most common symptom of HIT is enlargement or extension of a previously diagnosed blood clot , or the development of a new blood clot elsewhere in the body . This may take the form of clots either in arteries or veins , causing arterial or venous thrombosis , respectively . Examples of arterial thrombosis are stroke , myocardial infarction (" heart attack ") , and acute leg ischemia . Venous thrombosis may occur in the leg or arm in the form of deep vein thrombosis (DVT) and in the lung in the form of a pulmonary embolism (PE) ; the latter usually originate in the leg but migrate to the lung .

In those receiving heparin through an intravenous infusion , a complex of symptoms (" systemic reaction ") may occur when the infusion is started . These include fever , chills , high blood pressure , a fast heart rate , shortness of breath , and chest pain . This happens in about a quarter of people with HIT . Others may develop a skin rash consisting of red spots .

= = Mechanism = =

Heparin occurs naturally in the human body , but the development of HIT antibodies suggests heparin may act as a hapten , and thus be targeted by the immune system . In HIT , the immune system forms antibodies against heparin when it is bound to a protein called platelet factor 4 (PF4) . These antibodies are usually of the IgG class and their development usually takes about five days . However , those who have been exposed to heparin in the last few months may still have circulating IgG , as IgG @-@ type antibodies generally continue to be produced even when their precipitant has been removed . This is similar to immunity against certain microorganisms , with the difference that the HIT antibody does not persist more than three months . HIT antibodies have been found in individuals with thrombocytopenia and thrombosis who had no prior exposure to heparin , but the majority are found in people who are receiving heparin .

The IgG antibodies form a complex with heparin and PF4 in the bloodstream . The tail of the antibody then binds to the Fc?IIa receptor , a protein on the surface of the platelet . This results in platelet activation and the formation of platelet microparticles , which initiate the formation of blood

clots ; the platelet count falls as a result , leading to thrombocytopenia .

Formation of PF4 @-@ heparin antibodies is common in people receiving heparin , but only a proportion of these develop thrombocytopenia or thrombosis . This has been referred to as an " iceberg phenomenon " .

= = Diagnosis = =

HIT may be suspected if blood tests show a falling platelet count in someone receiving heparin , even if the heparin has already been discontinued . Professional guidelines recommend that people receiving heparin have a complete blood count (which includes a platelet count) on a regular basis while receiving heparin .

However , not all people with a falling platelet count while receiving heparin turn out to have HIT . The timing , severity of the thrombocytopenia , the occurrence of new thrombosis , and the presence of alternative explanations , all determine the likelihood that HIT is present . A commonly used score to predict the likelihood of HIT is the " 4 Ts " score introduced in 2003 . A score of 0 ? 8 points is generated ; if the score is 0 @-@ 3 , HIT is unlikely . A score of 4 ? 5 indicates intermediate probability , while a score of 6 ? 8 makes it highly likely . Those with a high score may need to be treated with an alternative drug while more sensitive and specific tests for HIT are performed , while those with a low score can safely continue receiving heparin as the likelihood that they have HIT is extremely low . In an analysis of the reliability of the 4T score , a low score had a negative predictive value of 0 @.@ 998 , while an intermediate score had a positive predictive value of 0 @.@ 14 and a high score a positive predictive value of 0 @.@ 64 ; intermediate and high scores therefore warrant further investigation .

The first screening test in someone suspected of having HIT is aimed at detecting antibodies against heparin @-@ PF4 complexes . This may be with a laboratory test of the ELISA (enzyme @-@ linked immunosorbent assay) type . The ELISA test , however , detects all circulating antibodies that bind heparin @-@ PF4 complexes , and may also falsely identify antibodies that do not cause HIT . Therefore , those with a positive ELISA are tested further with a functional assay . This test uses platelets and serum from the patient ; the platelets are washed and mixed with serum and heparin . The sample is then tested for the release of serotonin , a marker of platelet activation . If this serotonin release assay (SRA) shows high serotonin release , the diagnosis of HIT is confirmed . The SRA test is difficult to perform and is usually only done in regional laboratories .

If someone has been diagnosed with HIT , some recommend routine Doppler sonography of the leg veins to identify deep vein thromboses , as this is very common in HIT .

= = Treatment = =

Given the fact that HIT predisposes strongly to new episodes of thrombosis , it is not sufficient to simply discontinue the heparin administration . Generally , an alternative anticoagulant is needed to suppress the thrombotic tendency while the generation of antibodies stops and the platelet count recovers . To make matters more complicated , the other most commonly used anticoagulant , warfarin , should not be used in HIT until the platelet count is at least 150 x 10 ^ 9 / L because there is a very high risk of warfarin necrosis in people with HIT who have low platelet counts . Warfarin necrosis is the development of skin gangrene in those receiving warfarin or a similar vitamin K inhibitor . If the patient was receiving warfarin at the time when HIT is diagnosed , the activity of warfarin is reversed with vitamin K. Transfusing platelets is discouraged , as there is a theoretical risk that this may worsen the risk of thrombosis ; the platelet count is rarely low enough to be the principal cause of significant hemorrhage .

Various non @-@ heparin agents are used to provide anticoagulation in those with strongly suspected or proven HIT : danaparoid , fondaparinux , bivalirudin and argatroban . These are alternatives to heparin therapy . Not all agents are available in all countries , and not all are approved for this specific use . For instance , argatroban is only recently licensed in the United Kingdom , and danaparoid is not available in the United States . Fondaparinux , a Factor Xa inhibitor

, is commonly used off label for HIT treatment in the United States .

According to a systematic review , people with HIT treated with lepirudin showed a relative risk reduction of clinical outcome (death , amputation , etc .) to be 0 @.@ 52 and 0 @.@ 42 when compared to patient controls . In addition , people treated with argatroban for HIT showed a relative risk reduction of the above clinical outcomes to be 0 @.@ 20 and 0 @.@ 18 . Lepirudin production stopped on May 31 , 2012 .

= = Epidemiology = =

The exact number of cases of HIT in the general population is unknown . What is known is that women receiving heparin after a recent surgical procedure , particularly cardiothoracic surgery , have a higher risk , while the risk is very low in women just before and after giving birth . Some studies have shown that HIT is less common in those receiving low molecular weight heparin .

= = History = =

While heparin was introduced for clinical use in the late 1930s , new thrombosis in people treated with heparin was not described until 1957 , when vascular surgeons reported the association . The fact that this phenomenon occurred together with thrombocytopenia was reported in 1969 ; prior to this time , platelet counts were not routinely performed . A 1973 report established HIT as a diagnosis , as well as suggesting that its features were the result of an immune process .

Initially , various theories existed about the exact cause of the low platelets in HIT . Gradually , evidence accumulated on the exact underlying mechanism . In 1984 @-@ 1986 , John G. Kelton and colleagues at McMaster University Medical School developed the laboratory tests that could be used to confirm or exclude heparin @-@ induced thrombocytopenia .

Treatment was initially limited to aspirin and warfarin , but the 1990s saw the introduction of a number of agents that could provide anticoagulation without a risk of recurrent HIT . Older terminology distinguishes between two forms of heparin @-@ induced thrombocytopenia : type 1 (mild , non @-@ immune mediated and self @-@ limiting fall in platelet count) and type 2 , the form described above . Currently , the term HIT is used without a modifier to describe the immune @-@ mediated severe form .