



Heparin Induced Thrombocytopenia

**This course has been awarded
one (1) contact hour.
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Purpose and Objectives

The purpose of this course is to provide information to and educate caregivers about heparin induced thrombocytopenia (HIT), its potential for serious side effects, and the sequel of events that can result if the condition progresses or is improperly untreated.

Upon completion of this course you should be able to:

1. Describe normal clotting.
2. Define thrombocytopenia.
3. Define HIT.
4. Describe the types of HIT.
5. Define the underlying mechanism of HIT type II.
6. Identify the signs and symptoms of HIT.
7. Describe treatment for HIT.

Introduction

If you have ever provided care for a patient that is receiving heparin, chances are that you might not have been too concerned about the potential for the development of a blood clot. It only seems logical that heparin therapy would prevent the possibility of coagulation problems, especially if the patient is closely monitored by healthcare professionals.

Unfortunately there are a significant number of patients that have an even greater risk of developing a blood clot simply because of the administration of heparin therapy. These patients are at risk of developing a very serious condition called heparin induced thrombocytopenia (HIT).

This group of individuals will rely on you, the healthcare professional, to recognize the possibility of, and initial signs and symptoms of HIT, type I and type II. This course will focus on the most serious type, HIT type II immune response. To provide an increased understanding of HIT, a brief review of information about blood clotting, thrombocytopenia, the immune response and the actions of heparin precede the discussion about HIT.

Clotting and Coagulation

Normal clotting is essential to maintain homeostasis. In day to day life, small cuts and bruises we might sustain as we go about our activities of daily living aren't much of a distraction. We automatically rely on our body and its natural ability to heal minor injuries so that we can continue with our lives without worrying about a scraped knee or that scratch we got while playing with the family pet.

When our body systems are functioning normally and we begin to bleed, our body reacts by initiating a cascade of events to prevent injury, infection, and the threat of blood loss. This cascade involves clot formation, coagulation, inhibition of coagulation, and eventually dissipation of the clot.

The Clotting Cascade

The clotting cascade involves a series of events that take place along either an intrinsic (contact factor pathway) or extrinsic (tissue factor) pathway. Both pathways result in the formation of a fibrin clot.

The intrinsic pathway mechanism occurs in the absence of tissue injury and is due to an abnormal blood vessel wall. Clot formation that results from tissue injury occurs due to mechanisms involved in the extrinsic pathway.

Both pathways are complex and are initiated by different mechanisms but converge on a common pathway that results in clot formation.

The process of clotting, the repair of the injured tissue and the dissolution of the clot is known as hemostasis.

The clotting cascade is a series of reactions that result in the formation of a fibrin clot at the site of injury. The cascade is composed of an intrinsic, extrinsic, and a final common pathway.

Formation of a Fibrin Plug

During the process of platelet adhesion, Von Willebrand Factor (a blood glycoprotein involved in hemostasis) links collagen to platelets, forming a platelet plug. As events progress, platelets change shape and release various chemicals (including ADP and Thromboxane A₂) that propagate the coagulation cascade, so that clotting factors will localize at the site of injury.

In the presence of different catalysts (mainly enzymes and calcium), various clotting factors beginning with Factor XII (in the intrinsic pathway) and Factor VII (in the extrinsic pathway) are activated, ending in the activation of Factor X.

In the final common pathway, Factor X is converted to Factor Xa which combines with prothrombinase to eventually produce thrombin, fibrin, and finally a stable fibrin plug.

Hemostasis

Hemostasis is made up of four major events that occur (in order) after a vascular injury.

The events include:

1. Vascular constriction to limit blood flow to the area of the injury.
2. Thrombin, an enzyme that induces clotting by converting fibrinogen to fibrin, activates platelets. Platelets aggregate at the injury site to form a loose plug. The presence of fibrin helps stimulate the platelets to clump together. Platelets clump together by binding to collagen that has been exposed at the site of the injured blood vessel. Once platelets are activated, they release proteins that will activate additional platelets that are also important for the clotting cascade.
3. A fibrin mesh forms to hold the loose platelet plug in place. This is known as the clot.
4. Following tissue repair the clot must be dissolved before normal blood flow can return. The action of plasmin dissolves the clot (Marchesini & King, 2004).

Thrombocytopenia

Thrombocytopenia can be defined as any disorder where there are not enough platelets (thrombocytes) in the blood. A normal adult platelet count is usually somewhere between 150,000 to 450,000 per microliter of circulating blood (Mayo Clinic, 2010). Platelets are continuously being produced in the bone marrow and each platelet lives approximately ten days (Mayo Clinic, 2010).

A low platelet count that produces thrombocytopenia is often associated with abnormal bleeding and can be divided into three major causes:

1. Intravascular: Increased breakdown of platelets in the bloodstream
2. Extravascular: Increased breakdown of platelets in the spleen or liver
3. Low production of platelets in the bone marrow

Disorders that might involve low platelet production in the bone marrow include:

- Drugs such as heparin and chemotherapy
- Cancer such as leukemia in the bone marrow
- Aplastic anemia
- Infections in the bone marrow (A.D.A.M, 2005a)

Test Yourself

Thrombocytopenia associated with extravascular conditions involves increased breakdown of platelets in the:

- A. Bloodstream
- B. Spleen or liver
- C. Bone marrow
- D. Germinal matrix

The correct answer is B.

Risk Factors for Thrombocytopenia

Disorders that might involve intravascular breakdown of platelets in the blood stream may include:

- Pregnancy, which might cause mild thrombocytopenia, due to hemodilution.
- Idiopathic thrombocytopenic purpura (ITP), a condition that can occur when the immune system mistakenly identifies platelets as a threat and forms antibodies to attack them.
- Thrombotic thrombocytopenic purpura (TTP), a rare, life-threatening condition that occurs when small blood clots suddenly form throughout the body, using up large numbers of platelets. TTP can happen sporadically or as a side effect of some medications.
- Other auto-immune diseases that can destroy platelets such as rheumatoid arthritis and lupus.
- Blood poisoning (septicemia) from severe bacterial infections.
- Hemolytic Uremic Syndrome, a rare disorder that causes a sharp drop in platelets, destruction of red blood cells and impairment of kidney function.
- Disorders that involve intravascular breakdown of platelets in the liver or spleen such as an enlarged spleen which may trap platelets within the spleen, thereby decreasing the number of platelets in circulation.

The Immune Response

The immune response is the body's attempt to recognize and defend itself against substances that are interpreted as being foreign. Foreign substances are usually viewed as a possible threat to homeostasis and the body will react by trying to destroy them. These threats are called antigens and include viruses, bacteria, and other substances such as chemicals, drugs (e.g. heparin), and foreign particles (A.D.A.M, 2005b).

A healthy immune system recognizes antigens and destroys them. Although our own body cells have antigens in the form of proteins in cells, the body usually recognizes these as normal and does not generally react against them.

Occasionally the body does not recognize its own antigens and will begin to destroy them. This action can be observed in certain auto-immune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

Heparin

Heparin is used to diminish the clotting ability of blood and to help prevent clots from forming in the blood vessels. Heparin does not dissolve blood clots that have already formed, however it may prevent clots from becoming larger. Heparin also does not usually affect platelet count, unless HIT occurs (Baroletti & Goldhaber, 2006).

Heparin may be used to:

- Treat an existing deep vein thrombosis.
- Prevent blood clots in people who are at high risk such as those who have had blood clots in the past.
- Prevent a blood clot that can develop after surgery.

There are two types of heparin:

- Unfractionated heparin (UFH): given through a vein (IV), requires regular monitoring.
- Low-molecular-weight heparin (LMWH): can be self-injected at home (Cronin, 2006).

Test Yourself

Unfractionated heparin:

- A. Is the same as low-molecular-weight heparin.
- B. Can be self-injected at home.
- C. Required regular monitoring.
- D. Is supplied in an oral form.

The correct answer is C.

Adjusting Heparin Levels

While a patient is on heparin therapy, it is important to monitor for bleeding and other associated signs and symptoms of alterations in clotting time.

Baseline blood tests that are recommended prior to heparin therapy include:

- Complete blood count (CBC)
- International ratio (INR)
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)

Most facilities have policies and procedure guidelines for the administration of heparin that include timed lab draws to assess an individual response to heparin therapy.

Heparin Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) can be defined as a decrease in platelet count that can occur during or shortly after exposure to heparin.

HIT is considered to be the most important and most frequent drug-induced type of thrombocytopenia.

Did You Know?

Recent data show that up to 8% of heparinized patients will develop the antibody associated with HIT and that approximately 1–5% of patients on heparin will progress to develop HIT with thrombocytopenia, suffering from venous and/or arterial thrombosis in at least one-third of cases (Thrombosis Journal, 2005).

HIT can be associated with significant morbidity and mortality if it is allowed to progress unrecognized.

Incidence of Heparin Induced Thrombocytopenia

It has been estimated that 1% to 5% of patients treated with unfractionated heparin (UFH) will develop HIT (Cronin, 2006). HIT occurs less commonly in association with the administration of low-molecular-weight heparin (LMWH) products.

The majority of patients who develop HIT are 60 years or older. Data have suggested that females treated with UFH are at twice the risk of developing HIT than males (Cronin, 2006).

Patients treated with UFH who undergo orthopedic surgery are associated with the highest frequency of developing HIT.

Further, it has been demonstrated that a higher percentage of surgical patients will be diagnosed with HIT secondary to a thrombotic event when compared with medical patients.

Risk factors for the development of HIT include elderly post operative female patients treated with UFH.

Types of HIT

Two distinct types of HIT can occur:

- **Non-immune HIT (HIT Type 1 Non-Immune):** Is a benign form of HIT that occurs most frequently, and is characterized by a mild decrease in platelet count and is not associated with an increased risk of thrombosis. Was previously known as heparin-associated thrombocytopenia. This type of HIT affects up to 10% of patients under treatment with heparin and is characterized by a mild and transient asymptomatic thrombocytopenia (rarely less than 100,000 platelets/ μ L) that develops early (usually within the first two days of starting heparin) and disappears equally as fast once the heparin is stopped.
- **Immune-mediated HIT / Heparin -induced Thrombocytopenia Type II:** Is more uncommon than non-immune HIT, but is more dangerous, as it can cause much lower platelet counts and can result in the formation of venous and arterial clots with serious clinical symptomatology.

Paradoxically, despite a very low platelet count, patients who suffer from HIT are at risk for major clotting problems and thrombosis formation (Baroletti & Goldhaber, 2006). This type of HIT usually causes excessive blood clotting instead of bleeding, increasing the risk of developing clots deep within a leg blood vessel or the transport of such a clot to the lungs (Mayo Clinic, 2006).

More Info:

The mechanism underlying heparin-induced thrombocytopenia Type II is an immune response.

Onset of HIT

The onset of heparin-induced thrombocytopenia may be rapid or delayed:

- **Rapid Onset HIT:** In patients receiving heparin for the first time, the onset of thrombocytopenia usually occurs five to ten days after the administration of the heparin.
- **Delayed-onset HIT:** The thrombocytopenia occurs five or more days after heparin withdrawal.

The onset of clot formation in patients with HIT starts with a unique multi-molecular complex made up of heparin bound to a protein originating from platelets, known as platelet factor 4 (PF4).

Did You Know?

Patients that have received heparin in the past may have become sensitized and developed heparin-PF4 antibodies. These antibodies may decrease a patient's platelet count within hours after re-exposure to heparin! This is known as rapid onset HIT.

Pathophysiology of HIT

After heparin is administered to a patient, an immune complex can form between heparin and a specific blood factor, known as platelet factor 4, or "PF4", that is released by platelets (Baroletti & Goldhaber, 2006).

The body views this "heparin-PF4" complex as a foreign substance, and forms an antibody against the heparin-PF4 complex. The antibody binds to this complex and the platelets are destroyed (Baroletti & Goldhaber, 2006).

This disruption of platelets can lead to the formation of new blood clots in patients with immune-mediated HIT. The result can be a deep vein thrombosis (in the veins of the thigh or pelvis), pulmonary embolism, or even a heart attack or stroke.

Note! This formation of new blood clots does not seem to occur with the mild decrease in platelets, associated with non-immune HIT Type I (Baroletti & Goldhaber, 2006).

The Immune Response in Type II HIT

Researchers believe that the immune response to HIT is related to the chemical structure and size of unfractionated heparin (UFH) molecules. Due to the relatively large size and type of the molecules, UFH seems to cause the formation of immune complexes, such as those found with HIT.

HIT type II is mediated by a heparin-dependent IgG antibody. The primary antigen is a complex of heparin and platelet factor 4 (PF4).

As a result of the presence of heparin-like molecules (heparan sulfate) on the surface of endothelial cells, the HIT antibody-PF4-heparan sulfate complexes that form on the endothelial surface of the damaged blood vessel may cause further activation of the coagulation cascade and generation of thrombin.

Diagnosing HIT

The diagnosing of HIT is often made using both clinical and laboratory indicators. HIT can often be diagnosed by measuring the platelet count and PF4 antibody level in the blood (Baroletti & Goldhaber, 2006). The primary method for recognizing HIT is by routine monitoring of the platelet count in patients receiving heparin. A baseline platelet count prior to administering heparin should be obtained in order to evaluate for any changes.

The current recommendation is to obtain a platelet count at least every other day in patients receiving unfractionated heparin until day 14 or until the heparin is stopped. In patients considered by their physician to be a low risk, platelet counts should be evaluated at least every two to three days while receiving heparin therapy (Jang & Hursting, 2005).

Laboratory tests however may take extensive time to complete, thus delaying a diagnosis and potential treatment. Newer methods of predicting HIT are available, such as the “4 T’s” score (Thrombocytopenia, Timing, Thrombotic events, and other causes of thrombocytopenia) developed in 2003, and the “HEP” (HIT Expert Probability) score, developed by in 2010 (Cuker, Gimotty, Crowther, & Warkentin, 2012 & Joseph, Gomes, Al Solaiman, St John, Ozaki, Raju, et al., 2015). Both scoring systems quantify the clinical findings associated with HIT. In 2015 the Cleveland Clinic reported the first prospective comparison of these two scoring systems. The authors' main conclusion was that there was no difference between the 4Ts and HEP scores for predicting SRA+/EIA+ status. These tools are merely used as a guide for clinicians and should not substitute clinical judgment (Warkentin, 2015).

Type I HIT presents with bleeding and thrombocytopenia. Type II HIT usually presents with thrombosis and thrombocytopenia, which frequently leads to the recognition of HIT (Franchini, 2005).

Note! Under normal conditions, platelets do not clump together or aggregate when exposed to heparin.

Complications of Heparin Induced Thrombocytopenia

Thromboembolic complications can be venous, arterial, or both and include deep venous thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke, and occlusion of limb arteries.

However, the type and site of thrombosis depends on the patient's clinical profile.

Once HIT has been diagnosed and the heparin has been discontinued, the patient's platelet count usually starts to rise two to three days later and frequently returns to normal within four to ten days. The heparin-PF4 antibody will often disappear within two to three months after heparin therapy is stopped.

Future use of heparin, however, is frequently contraindicated (Franchini, 2005).

DIC as a Complication of HIT

Many healthcare professionals confuse HIT with Disseminated Intravascular Coagulation (DIC).

DIC is a pathological activation of coagulation (blood clotting) mechanisms that happens in response to a variety of diseases, and can be a complication of HIT (Becker & Brenner, 2011).

DIC leads to the formation of small blood clots inside the blood vessels throughout the body. As the small clots consume platelets, normal coagulation is disrupted and abnormal bleeding occurs. DIC can occur acutely but also on a slower, chronic basis, depending on the underlying problem. DIC results in widespread clotting with resultant bleeding. Regardless of the triggering event of DIC, once initiated, the pathophysiology of DIC is similar in all conditions (Becker & Brenner, 2011).

Treatment

Whenever HIT is suspected, heparin therapy should be stopped immediately, and can be reversed with protamine sulfate. However, stopping the heparin is not sufficient treatment for HIT, as it will not prevent clots from forming nor prevent subsequent thrombotic events, which occur in as many as 40–50% of the patients over the next several days or weeks (Franchini, 2005).

The appropriate treatment for HIT requires immediately removing the trigger (heparin) and controlling the thrombin storm of HIT by providing appropriate alternative anticoagulation medications. There are three non-heparin anticoagulants currently available that do not cross-react with HIT antibodies.

Medications available for alternative anticoagulation in HIT include:

- Argatroban
- Bivalirudin
- Fondaparinux
- Danaparoid
- Lepirudin
- Warfarin

These medications act immediately to either inhibit thrombin generation or inhibit thrombin directly.

In general, anticoagulation treatment is required for a minimum of 2-3 months to prevent recurrence of thrombosis.

Oral Anticoagulation

As previously noted, it is extremely important to stop heparin immediately and begin the use of an alternative anticoagulant once a diagnosis of HIT has been made.

Oral anticoagulation with warfarin should be started and continued until substantial platelet count recovery has occurred and while the patient is receiving a low molecular weight heparinoid and the thrombin-specific inhibitors, or a thrombin-specific inhibitor such as lepirudin and argatroban, with an overlap of at least five days (Franchini, 2005).

Recently it has become known that HIT patients who are switched to warfarin alone after the discontinuation of heparin may actually have worsening thrombosis and develop venous limb gangrene and skin necrosis.

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Test Yourself

HIT patients who are switched to warfarin alone after the discontinuation of heparin demonstrate rapid improvement.

- A. True
- B. False

The correct answer is False.

Case Study

Jill, a 68-year-old female was admitted to the hospital six days earlier with an acute anterior MI. To reduce her risk of thrombus formation her physician had placed her on intravenous heparin infusion. Much improved, Jill's plan of care indicates she should be ready for discharge tomorrow after the nurse educator meet with her.

That evening, Jill tells her nurse, Susan, that the back of her right calf hurts and feels warm to the touch, but the right foot feels cold. Susan performs a brief assessment and notes Jill's left foot is warm and pink, her pedal pulses (posterior tibial and dorsal) are easily palpable and that the capillary refill is less than two seconds. When Susan checks the right foot she is concerned by her findings: the pedal pulses are barely palpable, the foot is blanched, cool to the touch, and the capillary refill is greater than two seconds. Susan asks Jill if she is experiencing other symptoms such as shortness of breath or if she has noticed any bruising or blood in her urine. Jill denies this, and her lungs are clear on auscultation. Prior to calling Jill's physician, Susan checks Jill's lab reports and notes that over the past four days Jill's platelet count has decreased, and recognizes that this could be a case of HIT. She reports her findings to the physician. The physician orders a full work up to rule out deep vein thrombosis (DVT).

The patient will most likely not realize that her nurse's keen sense of reasoning and knowledge of HIT has possibly prevented her from developing a life threatening condition.

Conclusion

Heparin induced thrombocytopenia (HIT) is a common and serious complication of heparin therapy. Recognition of this potentially life threatening condition is essential.

By learning and applying new knowledge about the signs and symptoms of HIT, nurses play an instrumental role in preventing potentially devastating complications for patients that are currently receiving or who have just completed heparin therapy.

Familiarity with principles about blood clotting, thrombocytopenia, the immune response, and how the body might react to heparin therapy will help healthcare workers to identify any of their patients that might be considered to be at risk.

More information about HIT can be found at:

<http://www.heparininducedthrombocytopenia.com/index.asp>

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