Management of Heparin Induced Thrombocytopenia

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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 will be able to:

1. Describe the normal clotting cascade
2. Discuss thrombocytopenia
3. Describe the types of HIT and the underlying mechanisms of each type
4. Identify the signs and symptoms of HIT
5. Describe treatment management for HIT

Introduction

If you have ever provided care for a patient that is receiving heparin, chances are you have not been concerned about the potential for blood clot development. It only seems logical that heparin therapy would prevent the possibility of coagulation problems, especially when the patient is closely monitored by healthcare professionals. However, in a small percentage of cases, patients do develop clots in response to heparin treatment!

12 million individuals or 1/3 of all hospitalized patients are exposed to heparin annually. Of these patients 0.2% to 5% of these patients will develop a very serious condition called heparin induced thrombocytopenia (HIT).

- 20% of patients with HIT will die
- 10% of patients with HIT will suffer a major morbidity such as amputation

(Eke, 2018)

As a healthcare professional, you need the tools to recognize the 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 a thorough understanding of HIT, a review of coagulation, thrombocytopenia, the immune response and the actions of heparin will be provided.

Review:

Coagulation

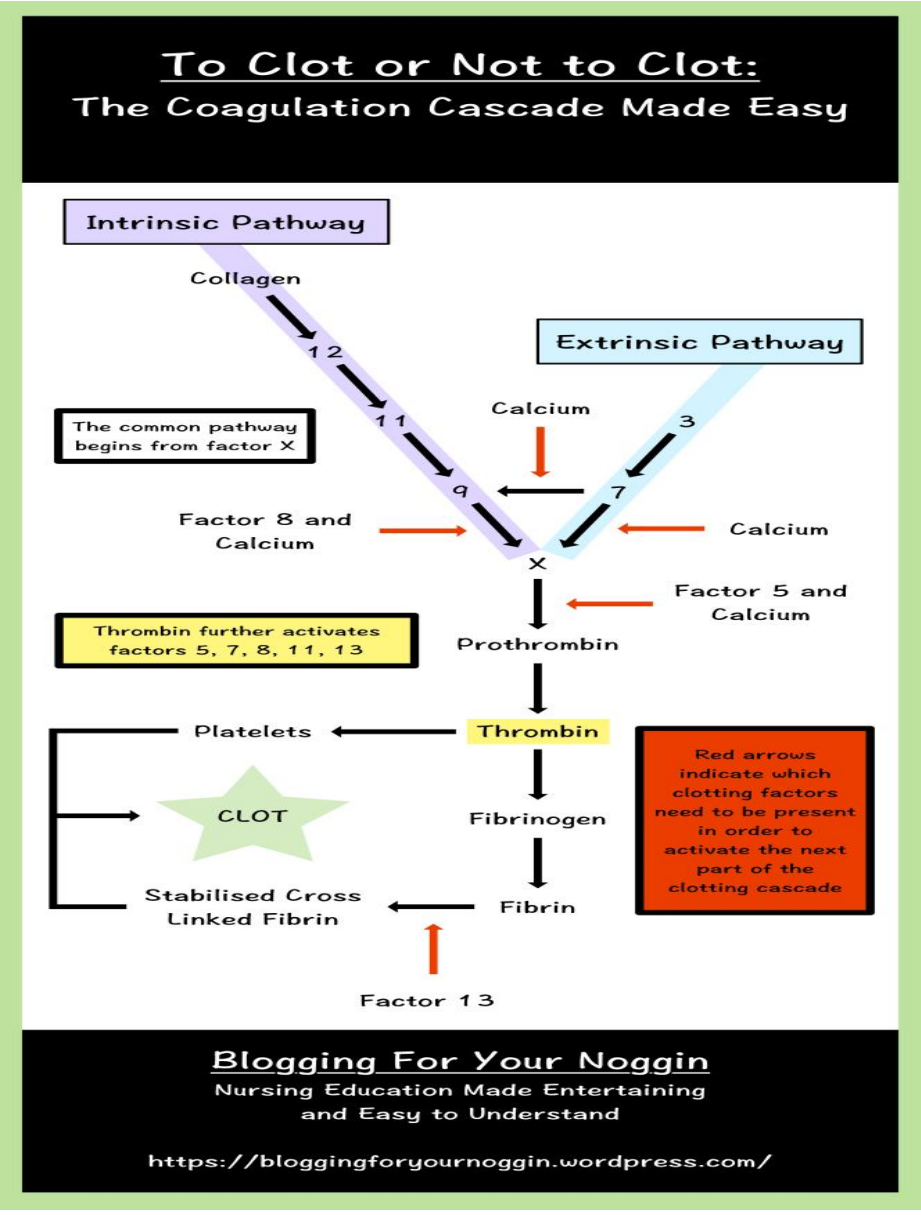
- Coagulation refers to the process of forming a clot to stop bleeding
    - Primary hemostasis:
        - Vasoconstriction: the first response to an injury in the vessel wall. The walls of the vessel constrict reducing blood flow to the injured area
        - Platelet plug: platelets merge on the site of injury developing a “plug” to slow the bleeding at the site,
            - Platelets are not enough to stop the bleeding, therefore, activate the next step-secondary hemostasis
        - Von Willebrand’s Factor promotes platelet stickiness
    - Secondary hemostasis:
        - Clot formation: Clotting factors activate each other in a process known as the clotting cascade resulting in a clot
            - Fibrinogen (soluble plasma protein) is divided into Fibrin (nonsoluble plasma protein) which stick together forming a clot

The Clotting Cascade

The clotting cascade involves a series of events utilizing an intrinsic and extrinsic pathway. Both pathways result in the formation of a fibrin clot.

- Intrinsic pathway:
  - Slower responding pathway
  - Occurs when there is trauma within the vessel
    - Is activated by platelets, exposed endothelium, collagen, or chemicals
- Extrinsic pathway:
  - Faster responding pathway
  - Activated by external trauma allowing blood to escape from the vessel
- Common pathway:
  - The intrinsic pathway merges with the extrinsic pathway to finish the clot formation

(Web.edu, ND)



Test Your Knowledge

How many patients who are hospitalized receive heparin therapy:

A. 10%
B. 20%
C. 30%
D. 40%

Rationale: 12 million individuals or 1/3 of all hospitalized patients are exposed to heparin annually. Of these patients 0.2% to 5% of these patients will develop a very serious condition called heparin induced thrombocytopenia (HIT).

- 20% of patients with HIT will die
- 10% of patients with HIT will suffer a major morbidity such as amputation

(Eke, 2018)

Thrombocytopenia

Thrombocytopenia is defined a low blood platelet count.

- Normal adult platelet count ranges between 150,000 to 450,000/microliter of circulating blood
- Platelets are continuously being produced in the bone marrow
- Platelets survive approximately ten days
- Symptoms or complications can occur when the platelet count is less than 10,000/microliters (Mayo Clinic, 2018)

Low platelet count causes

1. Increased destruction of platelets
2. Trapping of platelets in the spleen
3. Decreased production of platelets in the bone marrow
   (Mayo Clinic, 2018)

Causes:

Increased platelet destruction

- Pregnancy
- Autoimmune diseases
- Bacteremia
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Medications
  - **Heparin**
  - Aspirin
  - Quinine
  - Sulfa-containing antibiotics
  - Anticonvulsants

  (Mayo Clinic, 2018)

Trapping of platelets in the spleen

- The spleen may gather platelets from the blood stream while fighting an infection or during filtration resulting in a low circulating volume of platelets
  (Mayo Clinic, 2018)

Decreased production of platelets

- Leukemia
- Anemia
- Viral infections

- Chemotherapy drugs
- Heavy alcohol use

(Mayo Clinic, 2018)

Test Your Knowledge

Which of the following may decrease platelet production?

A. Pregnancy
B. Chemotherapy drugs
C. Enlarged spleen
D. Anticonvulsants

Rationale: Decreased production of platelets

- Leukemia
- Anemia
- Viral infections
- Chemotherapy drugs
- Heavy alcohol use

The Immune Response

The normal body immune response is to recognize and defend against substances that are interpreted as being foreign.

- Foreign bodies are identified as antigens
- The immune system produces antibodies against these antigens
- Result: destroyed foreign bodies

Autoimmune disorders:

- Normal body tissue is identified as a foreign body
- The immune system produces antibodies against normal body tissue
- Result: destroyed healthy body tissues

(U.S. National Library of Medicine, 2018)

Heparin

Heparin sodium is the drug of choice to prevent and reduce blood clot formation. Institutions have policies in place to prevent deep vein thrombosis (DVT) in all hospitalized patients. These policies include the use of devices and medications to combat the effects of immobility. Be sure to know and use the policies in place at your institution.

Heparin sodium is used in many situations to:

- Diminish the clotting ability of blood – post operative clot prophylaxis, heat attack
- Prevent existing clots from getting bigger – deep vein thrombosis, heart attack, pulmonary embolism
- Prevent clot formation – post operative clot prophylaxis

Heparin **does not**:

- Dissolve blood clots that have already formed.
- Usually affect platelet count, unless HIT occurs

There are two types of heparin:

- Low-molecular-weight heparin (LMWH):
  - Given subcutaneously
  - Part of a DVT prevention program
  - Can be used at home
- Unfractionated heparin (UFH):
  - IV administration
    - Continuous infusion
    - Intermittent dosing
  - Utilized for patients who have a history of clotting or atrial fibrillation
  - Can only be used in the hospital setting due to regular monitoring requirements
  - Drug of choice during emergencies such as stroke, heart attack, pulmonary embolism
  - Used prophylactically after long surgical procedures such as orthopedic or cardiovascular surgeries

Heparin Effects on the Clotting Cascade

Heparin works on the intrinsic and common pathway to inhibit reactions that lead to coagulation and development of fibrin clots.

Heparin:

- Inhibits thrombosis by inactivating factor X
- Inhibits conversion of prothrombin to thrombin
- Inactivates thrombin and prevents the conversion of fibrinogen to fibrin
- Inhibits the fibrin stabilizing factor prevention stable clot formation

Laboratory Testing

Heparin peak plasma levels are achieved 2-4 hours post administration

The body's ability to form clots is measured by a partial thromboplastin time (PTT). This test measures the amount of time it takes a blood sample to clot after being exposed to the chemical found in the laboratory test tube.

Timing and the correct amount of blood placed in the specialized tube is crucial for a correct reading that heparin administration adjustments can be made from.

Facilities will have policies and procedures to guide heparin administration. Know and follow your institution's procedures.

To learn more about heparin, please review RN.com's Hazards of Heparin course

Test Your Knowledge

The body's ability to clot after heparin administrations is measured by:

A. INR
B. PT
C. PTT
D. CBC

Rationale: The body's ability to ability to form clots is measured by a partial thromboplastin time (PTT). This test measures the amount of time it takes a blood sample to clot after being exposed to the chemical found in the laboratory test tube.

Heparin Induced Thrombocytopenia (HIT)

Heparin-induced thrombocytopenia (HIT) is a potentially lethal, immunologically-induced complication to unfractionated heparin therapy and to a smaller degree, low molecular weight heparin (Salter, 2016).

Rates of mortality and morbidity have decreased from 20% to 6-10% with improvements in early diagnosis and treatment (Eke, 2018).

HIT occurs when the body's immune system identifies platelet factor 4 (PF4) and heparin as foreign bodies and develops antibodies that bind to the complexes of PF4 and heparin. This binding action activates platelet production promoting a hyper-thrombotic state. Under these conditions, the platelets clump, reducing the number available in the circulation, and become clots which may wedge in veins and arteries.

HIT can manifest as a complication of heparin therapy in two ways.

- HIT Type I (Non-immune HIT):
    - Occurs: within the first two days of heparin exposure
    - Platelet count normalizes with continued heparin therapy
- HIT Type II (Immune-mediated HIT):
    - Occurs: 4-10 days of heparin treatment
    - Life & Limb threatening thrombotic complications

(Coutre & Crowther, 2018; Eke, 2018; & Salter, 2016)

NOTE:

When the term HIT is used in a hospital/medical setting, the term refers to HIT Type II (Immune-mediated HIT).

Why HIT is Different from Other Thrombocytopenias?

Hit is different from other types of Thrombocytopenias in two distinct ways.

- Bleeding is NOT a sign
- Venous and arterial thrombosis occur
    - Deep vein thrombosis (DVT)
    - Pulmonary embolism (PE)
    - Myocardial infarction (MI)

Risk Factors

It is estimated that 0.2% to 5% of patients treated with unfractionated heparin (UFH) will develop HIT (Eke, 2018).

HIT occurs in 0.1% of patients who have been treated with low-molecular-weight heparin (LMWH) products (Eke, 2018).

High-Risk factors include:

- The type of heparin used
    - UFH puts the patient at highest risk
- Surgical patients receiving thromboprophylaxis for greater than 5 days post-surgery
    - Orthopedic
    - Cardiovascular
    - Trauma
- Non-white races are 2-3 times more likely to get HIT
- Women are 1.7 times more likely than men to get HIT if treated with UFH

    - No difference was noted when LMWH was used
    - LMWH may have the greatest benefit in reducing HIT in post-surgical women
- Greater than 60 years of age
  (Eke, 2018, Salter, 2016)

Test Your Knowledge

HIT occurs when the body's immune system:

A. Identifies heparin and PF4 as foreign bodies
B. Identifies heparin as an antibody
C. Causes a hypo-thrombotic state
D. Causes a hyper-platelet state

Rationale: HIT occurs when the body's immune system identifies platelet factor 4 (PF4) and heparin as foreign bodies and develop antibodies that bind to the complexes of PF4 and heparin. This binding action activates platelet production promoting a hyper-thrombotic state. Under these conditions, the platelets clump, reducing the number available in the circulation and become clots which may wedge in veins and arteries.

Diagnosing HIT

Diagnosing HIT can be challenging, with both underdiagnosis and overdiagnosis posing serious potential adverse events.

- Failure to diagnose increases risk of:
    - Thrombosis
    - Amputation
    - Death
- Over or misdiagnosis can result in:
    - Major hemorrhage with thrombocytopenic patients treated with alternative anticoagulants
    - Thrombosis if heparin is discontinued unnecessarily

(Eke, 2018)

To make diagnosis less complicated, pretest scoring systems have been devised. Cuker and colleagues conducted a systematic review and meta-analysis of these scoring systems and their findings indicate that the 4Ts pretest scoring tool, was highly predictive for inclusion and exclusion for HIT (Eke, 2018). This tool is most commonly used as a diagnosis assistive tool.

NOTE: It is important that while this test is highly predictive, the researchers concluded that the testing for HIT should combine the 4Ts test and laboratory testing. Laboratory testing can identify HIT misdiagnosis.
(Eke, 2018)

A second more detailed tool HIT Expert Probability Score (HEP) improves on the diagnostic ability of the 4Ts tool but requires more prospective multicenter validation.

This module will discuss the 4Ts tool. The 4Ts tool is based on the characteristics of HIT and is has a numeric scale of 0-8 and is helpful to rule out HIT.

Feature	Score		
	2 points	1 point	0 points
Thrombocytopenia	>50% fall	30-50% fall	<30% fall
Timing of platelet count fall	Clear onset	Unclear onset	Fall without heparin

Thrombosis or other sequelae	New	Progressive	None
Other causes of thrombocytopenia	None	Possible	Definite
This table is based on the actual tool but is not intended for use with patients as all the component parts are not defined.			

Total scores and corresponding probability of HIT are as follows:

- 0-3: Low probability
- 4-5: Intermediate probability
- 6-8: High probability

The interactive tool in its entirety can be found at: https://www.mdcalc.com/4ts-score-heparin-induced-thrombocytopenia

Diagnosis: Considerations

HIT has three characteristics that distinguish it from other causes of thrombocytopenia. These are:

- Timing of the onset of thrombocytopenia – decreased platelet count
    - Decrease begins: 5-14 days of heparin treatment
    - Severity of thrombocytopenia: usually mild to moderate with platelet counts rarely less than 15,000/microliter
    - Occurrence of large-vessel thrombosis (venous or arterial)
        - Thrombosis precedes thrombocytopenia in up to 25% of HIT patients

Diagnosis: Laboratory Testing

- Immunologic assays – Enzyme-linked immunosorbent assay (ELISA)
    - Used to rule out HIT
    - Measures antibodies
- Functional assay - Serotonin Release Assay (SRA)
    - **Gold standard**
    - Measures the amount of serotonin release when exposed to therapeutic heparin dosing
    - Much more time consuming and more expensive; therefore, the ELISA test is recommended first

(Eke, 2018 & Salter, 2016)

Did You Know?

Under normal conditions, platelets do not clump together or aggregate when exposed to heparin but that they do when HIT occurs?

Often an algorithm or clinical practice document is developed using evidence-based practices to help guide diagnosis and treatment of patients with a specific disease process. One such clinical practice guideline comes from Ohio State University. This clinical practice document presented here as an example of what a facility can do to structure a HIT program. To see this document, go to: https://evidencebasedpractice.osumc.edu/Documents/Guidelines/HeparinThrombocytopenia.pdf

Treatment-Immediate

Treatment for HIT begins BEFORE laboratory confirmation.
When HIT is suspected:

- **STOP** all heparin products
    - This includes all heparin lock orders – if heparin is still used to keep these devices open
    - Low molecular weight heparin may need to be reversed using Vitamin K

        - Care must be used if Vitamin K is used to ensure that more clots do not form
- **Avoid** platelet transfusions
    - Exceptions:
        - Severe thrombocytopenia with bleeding
        - Patients undergoing invasive procedures with a high-risk of bleeding
- **Place** patients on alternative anticoagulation medications
    - Direct thrombin inhibitor (DTI):
        - DTI argatroban
        - DTI bivalirudin
        - DTI lepirudin (discontinued by manufacturer in 2012)
    - Warfarin
        - May cause microthrombi in patients with HIT and is not recommended until the platelet count has returned to normal
    - Other drugs may be available and being used; however, the ones listed have FDA approval for use in HIT
    -

Treatment-Long-Term

An alternative anticoagulation medication regime for patients with HIT should continue for at least 4 weeks. If HIT is complicated by thrombosis, treatment should continue for at least 3 months.

When converting to an oral anticoagulation agent, it is essential that the oral agent overlap the non-heparin agent for at least 5 days. Healthcare professionals need to be aware that the non-heparin agent can cause an elevation in the INR level independent of the oral anticoagulants' activity.

Patients who have experienced HIT should avoid the use of heparin in the future.

- Should the patient require heparin for a procedure, its use should be limited to during the procedure.
- Alternative anticoagulation medications should be used pre and post procedure for DVT prophylaxis

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 meets with her.

That evening, Jill tells her nurse 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 serious, potentially lethal complication of heparin therapy. Recognition of this potentially life-threatening condition is essential to reduce mortality and morbidity.

Familiarity with principles regarding blood clotting, thrombocytopenia, the immune response, will enable to healthcare worker to more thoroughly assess the patient on heparin to ensure early recognition and treatment of HIT.

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