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HEPARIN-INDUCED THROMBOCYTOPENIA: A REVIEW OF THE CLASSIFICATION, DIAGNOSIS AND TREATMENT

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ABSTRACT

Platelets comprise the blood plasma and are responsible for primary hemostasis that culminates in the formation of a platelet buffer. The standard value of the same in peripheral blood varies between 150,000 and 400,000 per cubic millimeter of blood. When this value becomes less than 150,000 per cubic millimeter of blood, thrombocytopenia occurs. Several drugs can generate this condition, but mainly heparin. The present study aims to review the literature highlighting the importance of early diagnosis and adequate therapeutic management of heparin-induced thrombocytopenia (HIT). A literature review was conducted in the electronic databases SciELO, LILACS and MEDLINE, between 2001 and 2018, using the descriptors thrombocytopenia, heparin, diagnosis and treatment. The HIT can be classified as type I and II, and type I is a non-immune thrombocytopenia related to a transient and benign reduction in the number of platelets per platelet aggregation and type II HIT occurs due to an immune reaction of type II hypersensitivity. The most common complications of HIT type II are venous thromboembolism, especially venous thrombosis and pulmonary embolism. The diagnosis should be raised in any patient with thrombocytopenia or thrombosis in confirming the use of this drug. Immediate discontinuation of heparin is mandatory in the face of clinical suspicion of HIT associated with anticoagulant therapy not heparin. In view of the above, it is concluded that the HIT mainly affects surgical patients who use heparin for more than four days for the prophylaxis of thromboembolic events. For this reason, if there is suspicion of HIT, early suspending the drug is mandatory, besides associating the non-heparin anticoagulation regimen.

KEYWORDS: Thrombocytopenia; Heparin; Anticoagulation.

INTRODUCTION

Platelets make up blood plasma and are responsible for primary hemostasis, interruption of bleeding through recruitment, adhesion to the injured vascular wall and secretion of substances that culminate in the formation of a platelet plug. Their standard value in peripheral blood ranges from 150,000 to 400,000 per cubic millimeter of blood. When this value becomes less than 150,000 per cubic millimeter of blood, what we call thrombocytopenia occurs. Several drugs can cause this clinical condition, such as ranitidine, beta-lactam antibiotics, vancomycin, and especially heparin.[1,6] Heparin is an unfractionated, acidic mucopolysaccharide with a molecular weight between 15000 and 18000. It inhibits blood clotting, as it potentiates antithrombin activity. As heparin is not absorbed from the gastrointestinal tract, it must be administered intravenously. It is inactivated in the liver, excreted in the urine and its half-life is one hour.[1,15] This drug potentiates the formation of complexes between antithrombin and activated clotting factors, thrombin and factors IXa, Xa and XIa. The formation of these complexes irreversibly inactivates these factors. In addition, heparin decreases platelet function2. It is divided into two subtypes: unfractionated and low molecular weight, which have a greater ability to inhibit factor Xa than the ability to inhibit thrombin and, in addition, interact less with platelets compared to unfractionated heparin. , reducing the risk of bleeding. It also has greater bioavailability and a long plasma half-life, which allows for a single daily administration, both for prophylaxis and treatment.[15] Heparin treatment is controlled by maintaining the activated partial

thromboplastin time (APTT) between one and a half to two and a half times the upper reference limit value according to laboratory variations. It is common to start treatment with dicumarines two days after starting heparin, and suspend it when the international normalized ratio (INR) is above two on two consecutive days.[6,8,15] Platelet activation resulting from the use of this anticoagulant results in an immunohematologic syndrome called heparin-induced thrombocytopenia (HIT). This disease occurs approximately five to ten days after starting the drug, and is characterized by a number of platelets lower than 150,000 per cubic millimeter of blood or a reduction greater than 50% of the basal number of platelets1,4. The present study aims to review the literature highlighting the importance of early diagnosis and appropriate therapeutic management of IHT.

MATERIAL AND METHODS

This is a descriptive study based on a narrative review of the literature, carried out between March and May 2018. The SciELO, LILACS and MEDLINE databases were consulted in search of articles that addressed pathophysiological, diagnostic and/or therapeutic aspects of thrombocytopenia induced by heparin between the period 2001 to 2018. For the survey of articles, the descriptors were used: thrombocytopenia, heparin, diagnosis and treatment and their correspondents in English: thrombocytopenia, heparin, diagnostic and treatment. The abstracts of the articles found were read and those that presented important information on the topic had the text analyzed in full for the preparation of this article.

RESULTS

A small drop in platelet count may occur in the first 24 hours of heparin treatment, as a result of platelet aggregation characterizing HIT.[2,5] This condition can occur during heparinization or after a short time of exposure to the drug, which can vary from five to 20 days20. Despite its low incidence, its occurrence is not rare due to the frequent use of this drug for prophylaxis of deep vein thrombosis, as well as its use in pregnant women who need anticoagulation, as it does not cross the placental barrier. Occasionally, there is a sudden drop in the count of patients previously treated with heparin.[6,7]

Any exposure to exogenous heparin can trigger HIT. The risk is up to ten times greater with unfractionated heparin than with low molecular weight heparin. Another important risk factor is the clinical context in which heparin is used. The greatest risk occurs in the postoperative period of cardiovascular and orthopedic surgeries, while obstetric surgeries have the lowest risk.[5,13]

IHT can be classified into types I and II (Chart 1). Type I HIT not related to immunological factors consists of a temporary and benign reduction in the number of platelets, being the most common form. Pathophysiology is based on the electrochemical characteristics of the drug molecule. Because heparin has a negative charge, it binds to platelets, which are positively charged, inducing platelet aggregation with subsequent sequestration of the platelet-heparin complex in the spleen, which results in platelet destruction. The decrease in the number of platelets does not have a relevant clinical-laboratory significance, since the amount can normalize regardless of whether or not heparin is interrupted.[8]

Table 1: Main differences between type I and II HIT.

properties	TIH Type I	TIH Type II
Gravity	Low	High
Start	1 to 4 days of heparinization	5 to 15 days of heparinization
Platelet Count	Up to 100,000/mm^3	30 to 80,000/mm^3
Mechanism	Pro-platelet aggregation	Immune reaction
Symptoms	Asymptomatic	Venous thromboembolisms and pulmonary embolism
Diagnosis	Clinical Heparin suspension	Laboratory Thrombocytopenia + antibodies heparin-dependent or heparin/PF4 antigens

Source: Adapted from Pavanelli MF, Spitzner FL (2011, p. 327).

The occurrence of type II HIT is based on the type II hypersensitivity reaction, also called antibody-mediated cytotoxic hypersensitivity. In this type of reaction, the IgM or IgG antibodies are autoimmune and bind to antigens present on the cell membrane. When heparin is administered, antibodies of the IgG class are produced and these bind to platelets through the Fc portion. This binding promotes the release of platelet factor 4 (PF4) by platelets. This PF4 has high binding affinity with heparin due to opposing electrochemical forces, that is, heparin has a negative charge while PF4 has a positive charge.

Thus, heparin binds to PF4, resulting in the formation of a highly immunogenic complex.[1,5,14]

This immunogenic complex resulting from the binding between heparin and PF4 is the antigenic target of IHT type II. The antibodies produced bind to the portions of PF4 that have been altered by heparin, promoting antigen-antibody interaction. This interaction takes place on the surface of platelets and endothelial cells. Consequently, there is platelet aggregation and destruction associated with endothelial injury and activation of this injured endothelium causing tissue factor release and activation of the coagulation cascade that promotes the synthesis of thrombin, the enzyme responsible for catalyzing the conversion of fibrinogen into fibrin for clot formation. Therefore, hemorrhagic diastasis can occur due to the massive reduction in the number of platelets as well as thromboembolic events caused by the prothrombotic state provided by the activation of the extrinsic coagulation pathway.[8,11,14]

The most common complications of type II HIT are venous thromboembolisms, especially venous thrombosis and pulmonary embolism. Arterial complications focus on involvement of the large arteries of the lower limbs leading to acute ischemia of the extremities. The most common arterial events are stroke and acute myocardial infarction. Arterial or venous thrombotic involvement depends on the patient's previous condition that led to the use of heparin: patients with cardiovascular disease tend to have arterial thromboembolic complications.[3,5]

Thrombosis can occur in unusual places in the body such as the cerebral venous sinus, splanchnic veins and venous circulation of the adrenal gland with consequent hemorrhagic bilateral adrenal necrosis. The appearance of thrombi in these locations is relevant since IHT is often associated as a causal factor. Thrombotic events as a whole are catastrophic, associated with a high rate of amputation and mortality, especially if the diagnosis is not made early.[13]

The diagnosis of HIT should be raised in every patient with thrombocytopenia or thrombosis using heparin, associated with the use of the Warkentin probability scale "4Ts" (Chart 2), which scores from zero to two within four different parameters : the first is a typical reduction in the number of platelets; the second is the reduction time after starting heparin use; the third is the presence of thrombotic events and the fourth consists of other probable causes for the reduction in the number of platelets.[9,13]

Table 2: Warkentin probability scale "4Ts" for HIT. Low probability (zero to three points), intermediate (four to five points) and high probability (six to eight points).

Thrombocytopenia	Platelet reduction < 30% or < $10x10^3$/Ul (zero point) Platelet reduction between 30-50% or 10-$19x10^3$/uL (one point) Platelet reduction > 50% or > $20x10^3$/Ul (two points)
Start time of thrombocytopenia	After 4 days of the first use of heparin (zero point) More than 10 days after starting heparin or if uncertain (one point) Start 5 to 10 days after starting heparin (colon)
Thrombosis or other sequel	No signs of thrombosis (zero point) Recurrent or progressive thrombosis, erythematous skin lesions at injection sites, or unconfirmed thrombosis. (a dot) Evidence of new thrombosis, skin necrosis, or acute systemic reaction after heparin bolus (colon)
Other cause of thrombocytopenia	Other definite cause (zero point) Other probable cause (one point) No other obvious cause (colon)

Fonte: Adapted from Cuker A, et al. (2012, p. 4163).

Patients classified as intermediate risk (four to five points) and high risk (six to eight points) are directed to laboratory tests to measure antibodies and to discontinue heparin with initiation of alternative anticoagulation. While patients at low risk (0 to 3 points) are exempt from antibody testing due to the high negative predictive value of this scale, which is sufficient to rule out the diagnosis of HIT.[9]

When there is clinical suspicion of HIT type I, the administration of heparin is discontinued. If there is normalization in the platelet count after the interruption, the diagnosis is established and, therefore, eminently clinical. In these cases, platelet counts should be monitored for at least ten days to ensure that type II HIT has not developed.[1,12]

When the platelet count does not reach normal within a few days after discontinuation of heparin or the patient presents thromboembolic events, the possibility of HIT type II must be taken into account, which must be confirmed by laboratory tests to identify antibodies. heparin-dependent or heparin/PF4 antigens. The immunoassay method capable of detecting the binding of antibodies to heparin-PF4 complexes is the enzyme-linked immunosorbent assay (ELISA).[2,5] Heparin-

dependent antibodies remain in serum or plasma for four to six months.[10,17]

In the therapeutic approach, the initial measure should be the replacement of heparin with an alternative anticoagulant therapy.[5,14,16] Continuing to use heparin can contribute to further increase the generation of thrombin, which can exacerbate thrombocytopenia and lead to the emergence of thromboembolic complications18. However, discontinuation of heparin is not the only course of action against IHT, being insufficient to avoid thrombotic complications or reduce mortality.[3,5,10]

There is no need for treatment for type I HIT. The platelet count usually normalizes within five days, even with continued use of heparin.[1] However, only drug withdrawal is not the only therapeutic measure when there are thromboembolic events such as in type II HIT.[3] As a therapeutic measure, protamine should be administered, which is a neutralizing agent that reverses the action of heparin.[9] It is also necessary to associate an alternative anticoagulant therapy. Among the pharmacological options available are non-heparin anticoagulants, direct and indirect thrombin inhibitors.[1,18]

As thrombin plays a fundamental role in the development of thrombotic complications in IHT, the essential treatment for such manifestations should include a drug that reduces thrombin synthesis.[6,7] Recombinant hirudin is the most specific direct inhibitor of thrombin with two major advantages: it is not inactivated by PF4 and does not show cross-reactivity with heparin.[19] Argatroban, which is also a direct inhibitor, has rapid antithrombotic therapeutic efficacy, causing minimal risk of bleeding and rapid restoration of hemostasis when its use is discontinued.[1,9] Sodium danaparoid is an indirect thrombin inhibitor that shows in vitro cross-reactivity with heparin-associated antiplatelet antibodies and has no available antidote, thus being avoided.[10,16]

Warfarin is a coumarin that antagonizes vitamin K, resulting in decreased activity of vitamin K-dependent factors II, VII, IX, and X. After administration of this oral anticoagulant, factor VII levels drop dramatically within 24 hours, but the factor II, which has a long half-life, decreases by only 50% of normal in three days and, therefore, only after this period will the patient be anticoagulated15. It could be an option for alternative anticoagulation, but it can cause more serious clinical outcomes than heparin itself, such as skin necrosis, gangrene, and even aggravation of preexisting thrombosis by promoting a drop in protein C levels, a natural anticoagulant that inhibits the blood clotting process. thrombin generation.[13]

Low molecular weight heparin is contraindicated because it presents cross-reactivity in vitro with the antibodies formed, a situation that leads to the persistence of thrombocytopenia, as well as to the occurrence of new or recurrent thrombotic events. Plasmapheresis can be used as an associated therapy, especially in patients with type II HIT, to assist in the removal of immune complexes5. It is a safe method that can reduce mortality within the initial four days of thrombocytopenia.[10,13] Thrombolytic therapy is also an alternative route, but little used because of the frequent occurrence of intracerebral hemorrhage.[8]

Preventive measures can prevent the occurrence of IHT. The replacement of unfractionated heparin with low molecular weight heparin is one of them, in addition to the use of new direct oral anticoagulants (DOACs) for prophylaxis and primary treatment of thrombosis: direct thrombin inhibitors (dabigatran) which, because they do not bind to other proteins promote low pharmacokinetic and pharmacodynamic limitations in addition to not having an antiplatelet effect; factor Xa inhibitors (rivaroxaban) that inactivate free factor Xa and incorporated factor Xa and do not interact with the antithrombin inhibitor.[21] Laboratory monitoring of the platelet count can be performed, although 2 to 5% of the monitoring involves IHT.[13,17]

DISCUSSION

Thrombocytopenia is a common condition, despite its low incidence, characterized by a reduction in the number of platelets in the bloodstream. It usually affects patients undergoing surgical procedures that use heparin for prophylaxis of thrombotic events.[2,7] These two major rationales were emphasized in all studies in order to explain why heparin-induced thrombocytopenia was addressed.

A literature review emphasized that there are numerous causes for IHT, including pharmacological ones. Heparin was approached because it is a drug widely used in the hospital environment and because it is associated with catastrophic outcomes when it causes thrombocytopenia. IHT is more associated with the use of unfractionated heparin than with low molecular weight heparin. They used the incidence of IHT cases in hospitals as a basis and observed that patients who developed it were using unfractionated heparin. The use of this drug in the postoperative period of major cardiac and orthopedic surgeries concentrates the highest occurrence of IHT.[5,13,15] In other words, the use of unfractionated heparin in the postoperative period of major surgeries has a very high risk for the development of thrombocytopenia.

The division of its two subtypes is fundamental for the understanding of its pathophysiology that guides diagnostic and therapeutic methods. Type I HIT develops mildly through a non-immune reaction and rarely progresses to serious complications. Type II, on the other hand, has more severe characteristics because its pathophysiology is an immunological reaction of type II

hypersensitivity with the formation of heparin-dependent antibodies with thromboembolic complications that must be carefully managed.[8,11]

The methods used to diagnose IHT are divided into clinical and laboratory. The clinical diagnosis is relevant and should always be performed first with the aid of the Warkentin "4Ts" probability scale, which assesses the reduction in the number of platelets; the time of reduction after starting heparin use; the presence of thrombotic events and whether there are other probable causes for the reduction in the number of platelets.[9,13] As it has a high negative predictive value, patients classified as low risk have the possibility of IHT excluded, while patients classified as intermediate or high risk are directed to discontinue the use of heparin and perform laboratory tests.[5,10]

If there is normalization of platelet count after heparinization is stopped or spontaneously without discontinuation, the diagnosis prevails for type I HIT of a benign nature. In these cases, platelet counts should be monitored for at least 10 days to ensure that thrombocytopenia has not persisted.[16]

When the platelet count does not normalize after these 10 days, even with heparin discontinuation, or the patient presents thromboembolic events, type II HIT is suspected.[9,12] Laboratory tests allow the identification of heparin-dependent antibodies. The immunoassay method commonly used to diagnose HIT type II is the "Enzyme-linked Immunosorbent Assay" (ELISA) because it is easily performed.[2,8]

For patients who develop thrombotic events, usually with type II HIT, heparin suspension alone is not the most appropriate course of action. These patients should receive protamine sulfate (or hydrochloride) that neutralizes the action of heparin and an alternative anticoagulant therapy.[1,3,18] Low molecular weight heparin, as it is associated with a lower occurrence of IHT, could be an option, however, its reactivity in vitro with heparin-dependent antibodies has been proven in order to perpetuate the thrombocytopenia.[5,8] Coumarins, especially warfarin, should also be avoided because they cause more drastic consequences than heparin itself, such as skin necrosis and gangrene.[13,15] A safe option, according to the studies, would be direct thrombin inhibitors, such as argatroban, as they do not present cross-reactivity with antibodies.[19]

IHT, a little-known condition and surrounded by disagreements regarding its clinical, diagnostic and therapeutic aspects, can be prevented through the use of DOACs that have been gaining ground over the years through scientific studies because they do not induce IHT, have no effects. antiplatelet agents and because they do not interact with the antithrombin inhibitor.[17]

FINAL CONSIDERATIONS

It is an extremely relevant topic for all its aspects, but little knowledge in medical practice. This condition is reflected by the difficulty in obtaining scientific articles on the subject in the search for this study. However, the articles found within the inclusion criteria addressed the theme without major divergences, so that they acted as a complementary source of information. Because of this, hematology-based books were also included in the database.

Future studies that address this issue may place greater emphasis on the clinical aspects of IHT, associating the differences between type I and type II, so that recognition in the hospital environment can be objective and early, allowing for the discontinuation of heparin and initiation of an alternative anticoagulant therapy. thus avoiding serious repercussions for the patient.

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