Rivaroxaban for the treatment of Heparin-induced Thrombocytopenia with Thrombosis in a patient undergoing artificial hip arthroplasty: A Case Report

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Abstract

BACKGROUND
Anticoagulation treatment after lower limb surgery is one of the key methods to avoid thrombosis, and low-molecular heparin is the treatment that is most frequently used in clinical practice. But one uncommon side effect of low-molecular heparin is HIT, which can develop into thrombosis if not caught early enough or managed incorrectly.

CASE SUMMARY
We present a case of a patient who underwent hip arthroplasty and experienced thrombocytopenia due to heparin-induced thrombocytopenia on the ninth day following the application of low-molecular heparin anticoagulation. We did not diagnose HIT in time and applied 1u of platelets to the patient, which led to thrombosis. Luckily, the patient recovered following effective and timely surgery and a significantly alter to Rivaroxaban.

CONCLUSION
Patients using low-molecular heparin after lower limb surgery need to have their platelet counts regularly checked. If heparin-induced thrombocytopenia develops, platelet treatment should be given with caution.
INTRODUCTION

Heparin, a commonly used anticoagulant, has a significant clinical status, including unfractionated (UFH) and low molecular weight heparin (LMWH). For the first time, McLean purified heparin from dog liver in 1918. Heparin has increasingly gained in popularity since that time. A smaller-molecular-weight heparin fragment known as LMWH was first discovered in 1976 and was produced by UFH either chemically or through enzymatic depolymerization. The pharmacokinetics of LMWH are more stable, it has a longer half-life, better bioavailability, better absorption after subcutaneous injection, and it causes less adverse effects. Heparin-induced thrombocytopenia is a serious adverse medication reaction that is characterized by thrombocytopenia and thrombosis. About 35% of patients worsen the occurrence of heparin-induced thrombocytopenia with thrombosis (HIT), which has certain disability and fatality rates. The incidence rate is between 1% and 5%. In individuals with HIT, platelet levels rarely drop below 20*10^9/L, and bleeding is uncommon. Furthermore, regular preventive platelet administration is not advised to reduce the chance of thromboembolism, direct oral anticoagulants (DOACs) should be used preferentially in HIT patients with stable vital signs and a moderate to low risk of bleeding, according to the American Society of Hematology’s (ASH) therapeutic guidelines for venous thromboembolism (VTE) in HIT treatment published in 2018. A DOAC with predictable pharmacokinetics and pharmacodynamics, rivaroxaban is a factor Xa inhibitor. Specific thromboembolic illnesses can be treated with Rivaroxaban based on the findings of the Phase III trial. The writers describe a patient with HIT who was misdiagnosed and improperly treated, but who was ultimately effectively rescued by aggressive surgery and replacement of Rivaroxaban.

CASE PRESENTATION

Chief complaints
On October 9, 2022, a female, 78Y, underwent an admission owing to "Pain in both hip joints for 2 years and aggravated for 1 mo."

**History of present illness**

Two years ago, the patient had no obvious cause of intermittent pain in both hip joints, which worsened after activity and could be slightly relieved after rest. No special diagnosis and treatment were performed. When the pain worsened, he was given Nonsteroidal anti-inflammatory drug by himself; A month ago, the patient experienced worsening pain in both hip joints, with a continuous increase in events and an inability to relieve the pain on their own. In order to seek further diagnosis and treatment, they came to the hospital for treatment. On October 11, after ruling out the surgical contraindication, the patient agreed to hip replacement. Following surgery, the patient received 5000WU LMWH sodium as anticoagulant treatment. Due to diabetic ketoacidosis, the patient was sent to the Department of Intensive Medicine on October 12. Meanwhile, LMWH was halted, a common sodium heparin injection was utilized to remove 0.625wu from the pipeline. Then, the patient was moved to the Department of Endocrinology for additional care on October 14 when her vital signs stabilized. The D-dimer was tested after admission for 0.71ng/L and platelet 212*10^9/L. The daily anticoagulant treatment with LMWH sodium of 5000WU is adequate, and the blood routine test, coagulation routine test, and other indicators were frequently checked, taking into account the patient's health as a whole.

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**History of past illness**

The patient had a 3-year history of diabetes and a 3-year history of coronary artery disease.

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**Personal and family history**

The patient had no specific personal and family history.
**Physical examination**

On admission for physical examination, the patient's blood pressure was 131/89 mmHg and a pulse rate of 68 beats per minute. The patient's lungs were auscultated clearly, with normal heart sounds and no murmurs during auscultation.

**Laboratory examinations**

These modifications in D-dimer and platelet levels are tracked (Figure 1). The IgG antibody linked to HIT had a detection result of 2.49 optical density units on October 31 (reference value: 0.4 optical density units).

**Imaging examinations**

Imaging evidence collected during percutaneous arteriography is shown in Figure 2.

**FINAL DIAGNOSIS**

Heparin-induced thrombocytopenia with thrombosis.

**TREATMENT**

The daily anticoagulant treatment with LMWH sodium of 5000WU is adequate, and the blood routine test, coagulation routine test, and other indicators were frequently checked, taking into account the patient's health as a whole. D-dimer was 14.4ng/L on October 17, thus a 5000wu LMWH sodium injection was given twice a day. D-dimer readings were 17.15ng/L and 54*10^9/L for platelets on October 19, and right lower pulmonary artery thrombosis was detected by pulmonary artery CTA, additionally, an ultrasound of the lower extremities revealed no thrombosis in the arteries or veins of either lower extremity. The patient's platelet count continued to decline with the addition of 5mg of warfarin sodium tablets once day, reaching 25*10^9/L on October 21. The hematology department recommended administering a 1u platelet transfusion, and 67*10^9/L of platelets were measured on October 22. At the night of October 21, the patient experienced edema and coldness in the left lower limb, which got worse in the
morning. On October 22, an improved vascular ultrasound revealed that the left iliac artery's local blood flow was absent, the left lower limb artery's blood flow velocity was reduced, and thrombosis was possible. On October 22, the patient had an arteriogram of the left lower limb, which showed thrombuses in tibiofibular trunk and the distal of common iliac artery(Figure 2AB). During the operation, three white thrombi were suctioned out of the common iliac artery and the tibiofibular trunk was injected with 20wu urokinase, the outcome of which is shown in the Figure 2C. Later, a thrombolytic catheter was placed in the common iliac artery(Figure 2D), and the patient returned to the ward. October 24, The iliac artery thrombuses became smaller in the repeat angiography(Figure 2E). We then did a femoral artery thrombectomy, removing two white thrombi, and evaluated the imaging for the left common iliac artery and internal/external iliac arteries(Figure 2F). Thrombocytopenia started on the ninth day after using heparin, 4T's score was 8 points, which is a high clinical possibility of HIT. So, from October 10 to October 28, we stoped administering LHWH and started giving Rivaroxaban 15 mg every 12 h.

OUTCOME AND FOLLOW-UP
The patient was released on November 11 when his general health appeared to have stabilized. After discharge, the patient continued with the current plan of full course anticoagulation therapy, and no significant abnormalities were found in the monitoring of blood routine and coagulation routine. We also informed the patient that she should not use heparin under any circumstances in the future.

DISCUSSION
HIT is an unfavorable heparin reaction caused by antibodies when heparin medicine is administered. A decline in blood platelet count is the primary clinical sign of HIT, which in extreme situations can result in arteriovenous thrombosis and mortality. Type I and Type II HIT can be distinguished by their mechanisms, onset times, treatments, and prognoses. 10% to 20% of people will get type I HIT, which typically happens 1-2
days after starting heparin. Typically, the drop in blood platelet count does not fall below $100\times10^9/L$, which prevents thrombus and bleeding. Withdrawal or particular care are typically not necessary. Immunity is connected to type II HIT. Its primary characteristic is the considerable reduction in blood platelet count, which may also be accompanied by a serious risk of thromboembolism. The most common reasons for death and disability in HIT patients are among them, specifically thrombosis and embolism problems. HIT accounts for 20%-30% of amputations and fatalities.\(^7\)

Platelet factor IV (PF4) is a protein that the body's platelets release in response to heparin. PF4 can combine with heparin to create the H-PF4 complex and connect to the platelet membrane simultaneously. The H-PF4 complex possesses immunogenicity in some people, which causes the development of an anti-H-PF4 antibody.\(^9,10\) A bigger immune complex can be created by combining the anti-H-PF4 antibody with the H-PF4 complex and the F(ab)2 fragment. To activate platelets, the immune complex first interacts with the Fc fragment on the surface of the platelet membrane. Numerous substances are released by the active platelets, prompting more platelet activation and aggregation. Additionally, the body's thrombin and platelet-derived microparticle levels rise at the same time, which lowers platelet counts and causes a hypercoagulable state.\(^8\) There are currently no internationally accepted diagnostic standards for HIT. The standard method for diagnosing ideas is to use the 4T's score, dynamic platelet monitoring, HIT antibody detection, and/or platelet function test as a basis for the diagnosis.\(^11,12\)

The four factors that contribute to thrombocytopenia are reduced platelet production, increased platelet intake and destruction, abnormal platelet dispersion, and haemodilution. Increased platelet breakdown caused by immunological elements leads to HIT. As a result, platelet transfer without stopping heparin can worsen the situation and even cause thrombosis. In this case, the patient's platelet count was $54\times10^9/L$ on the ninth day since starting heparin treatment, and the pulmonary artery CTA revealed a pulmonary embolism on the tenth, but the patient exhibited no clinical signs. We should be on the lookout for HIT immediately, but the identification was delayed
because of our limited knowledge of the disease. On day 11, 1U platelet was administered, next the patient experienced lower extremities arterial thrombosis on day 12. After multiple consultations and literature review, HIT was finally diagnosed and the patient was eventually removed from danger after surgery and application of NOACs. Rivaroxaban was used in place of heparin for anticoagulation since it not only had an immediate and potent anticoagulant action but also did not make the situation worse.

Rivaroxaban is a new oral anticoagulant, this medication contains an FXa inhibitor. A serine protease called FXa is found upstream of the blood agglutination response. It can be found at the intersection of the pathways that connect internal and exterior activation. FXa has the ability to suppress external as well as endogenous coagulation. In blood agglutination reactions, thrombin's principal rate-limiting product, FXa, has the ability to magnify biological signals. 138 thrombin molecules can have their biological activities inhibited by a single FXa inhibitor.13 As a result, FXa theoretically has a greater anticoagulant impact than thrombin inhibitor. A recently created tiny molecule with a strong affinity for the Xa factor is called rivaroxaban. After combination, it can directly block free FXa activity as well as Xa activity. Rivaroxaban's action is distinct from that of LMWH and does not require the involvement of other components.14 Additionally, Rivaroxaban does not require injection or blood coagulation function monitoring.

Clinical evidence of NOACs in HIT patients has not yet been published in a significant prospective trial. Rivaroxaban's capacity to arrest platelet decline after HIT has been substantiated by an increasing number of small studies and case reports in recent. A prospective study conducted in 2016 by Linkins LA et al16 revealed that 7 of the 12 HIT patients had had heparin treatment for 1-3 days, 90% of patients' blood platelets steadily increased with rivaroxaban therapy; In 2017, Warkentin T and his team17 discovered that only one of the 16 HIT patients who received Rivaroxaban treatment had their condition worsen; The efficiency and safety of Rivaroxaban in HIT were further validated by the prospective investigation of Cirbus K and others16;
According to the 2018 ASH management guide on VTE in HIT treatment, it is advised to begin strong anticoagulation in patients with acute HIT, and Rivaroxaban should be administered at a dose of 15 mg twice daily for three weeks before increasing to 20 mg once day. The incidence rate of HIT varies according to the patient population and heparin exposure. According to the patient's condition, he has been exposed to heparin after hip joint replacement and given low molecular weight heparin at a therapeutic dose. Additionally, the Department of Intensive Care used the UFH wash pipe during therapy. Additionally, there was a progressive decrease in platelet level that was greater than 50% on the ninth day after starting heparin. On the first day, a progressive fall in platelet count started, with a decline of more than 50%. A freshly developed common iliac artery thrombosis was found. The score of 4Ts was 8 and the HIT-related IgG antibody was 2.49 optical density units after factors such thrombotic thrombocytopenic purpura, immune thrombocytopenic purpura, drug and infection-related thrombocytopenia, and immunological thrombocytopenic purpura were disregarded. It was established that HITT existed.

Heparin therapy should be stopped right away after HIT has been identified or is strongly suspected, especially in patients who have HITT or who are at risk for subsequent thrombosis. Hemorrhage is uncommon, and the blood platelet count in HIT patients is rarely lower than 20*10⁹/L. To reduce the risk of thromboembolism, routine platelet transfusion is not advised. If a platelet transfusion is required, it must be performed after the heparin has been stopped. The patient did not discontinue taking LMWH during the early stages of thrombocytopenia due to the possibility of pulmonary artery thrombosis and significant surgery following the initial thrombocytopenia. Arterial thrombosis was found after 9 days, the HITT diagnosis was deemed conclusive following a study of the literature and interdisciplinary consultation. The patient started taking Rivaroxaban 15mg daily three days after the arterial thrombus was removed.

The COVID-19 pandemic has rapidly spread around the world and is still widespread today. Given the tremendous effects the pandemic has had on people, it is
still challenging to predict when it will cease. New obstacles to prevention and control arise as a result of the novel coronavirus's shifting epidemiological tendencies both domestically and internationally. LMWH or regular heparin anticoagulation therapy can be administered without risks for medium-sized cases with risk factors for severe disease and quick disease progression, as well as heavy and critical cases, according to national and international standards and associated consensus. After excluding out thrombotic comorbidities, the ASH and the CHEST both advise using preventive dosages of anticoagulants in patients with newly diagnosed severe and acute coronary disease. However, it is still important to monitor changes in the patient's platelet counts while they are receiving therapy for pneumonia. When a progressive decline in platelet levels occurs and HIT is highly suspected after other relevant risk factors have been excluded, appropriate treatment should be given promptly, and HIT-related IgG antibody testing should be completed if available.

**CONCLUSION**

In the clinic, we should be on the lookout for HIT in patients who have used heparin and have thrombocytopenia. The HIT antibody test should be run to diagnose HIT when the clinical assessment of the 4T's score is moderate or severe. In this instance, HITT and secondary arterial thrombosis also happened. Heparin was replaced with Rivaroxaban for anticoagulation since it not only had a quick and effective anticoagulation effect but also did not worsen the condition. In the meanwhile, this example offers some clinical proof that the NOACs can be used to treat HIT both initially and long-term. However, the path is still blocked, and large-scale clinical investigations are required to produce pertinent data that will help direct the course of treatment.
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