Heparin Induced Thrombocytopenia - Thrombosis Due to Low Molecular Weight Heparin in Orthopedic Patients

Dede ŞİT*, Abdullah ALTINTAŞ, Ali K. KADİROĞLU***, Hasan KAYABAŞI***, Mehmet SUBAŞI****, Abdurrahman IŞIKDOĞAN*****, M. Orhan AYYILDIZ****

* Dicle University, Department of Nephrology
** Dicle University, Department of Hematology
*** Dicle University, Department of Internal Medicine
**** Dicle University, Department of Orthopaedic Surgery
***** Dicle University, Department of Oncology, DİYARBAKIR

ABSTRACT

Heparin is a drug that is widely used for prophylaxis of thrombosis or treatment in many clinical situations, particularly in surgical clinics and Heparin-induced thrombocytopenia (HIT) is the most important and most frequent drug-induced and immun mediated thrombocytopenia in patients receiving heparin, and has significant morbidity and mortality An early, transient, and mild thrombocytopenia is seen in many patients after initiation of heparin. Heparin induced thrombocytopenia is caused by IgG antibodies that recognize multimolecular complexes of platelet factor 4 (PF4) and heparin. Many studies suggest that up to 8% of heparinized patients develops the HIT antibodies, approximately 1–5% develops HIT with thrombocytopenia, and at least one-third of cases develops thrombosis. In addition thrombosis in HIT is associated with a mortality rate of approximately 20–30%. This complication not only ocur with U Fractioned Heparin (UFH) treatment but also with low molecular weight heparine therapy. In recent study, thrombocytopenia associated with low molecular weight heparins (LMWH) was evaluated prospectively in 340 orthopedic patients who received LMWH for prophylaxis during elective surgery. HIT developed in only 1.2% patients (4/340) and femoral vein thrombosis occurs in 1 patient with HIT. Platelet count recovery was seen in 4 patients after LMWH cessation. In conclusion, HIT is not only a common but also a serious complication of heparin therapy with a high rate of morbidity and mortality. In addition it does not seen only by intravenous/subcutaneous UFH but also by subcutaneous LMWH therapy and the clinicians must be aware of this syndrome in their heparin receiving patients.

Key Words: Low molecular weight heparins, Thrombocytopenia, Orthopedic patients

ÖZET

Ortopedik Hastalarda Düşük Molekül Ağırlıklı Heparine Bağlı Trombositopeni-Tromboz

Heparin, özellikle cerrahi kliniklerde olmak üzere, tromboz proflaksisi ve bazı klinik durumların tedavisinde yaygın olarak kullanılan bir ilaçtır. Heparin ilişkili trombositopeni (HIT) heparin alan hastalarda ilaca bağlı ve immün aracılıklı gelişen en sık ve en önemli trombositopeni nedeni olup ciddi morbidite ve mortaliteye sahiptir. Bazı hastalarda heparine başlandıktan hemen sonra erken, geçici ve ılımlı bir trombositopeni görülebilir. Platelet faktör IV (PF4) ve heparin multimoleküler kompleksine karşı gelişen Ig G antikorları HIT oluşumuna neden olur. Bazı çalışmalarda heparinize edilen hastaların %8'inde HIT antikorları, yaklaşık %1-5'inde HIT ile birlikte trombositopeni ve en az vakaların 1/3'ünde tromboz geliştiği ortaya konmuştur. Bununla birlikte HIT'de tromboz, yaklaşık %20-30 ölüm oranına sahiptir. Bu komplikasyon sadece unfraksiyone heparin (UFH) ile tedavide değil aynı zamanda düşük molekül ağırlıklı heparin (LWMH) kullanımında da ortaya çıkabilir. Bu çalışmada elektif cerrahi girişim için proflaktik olarak LWMH alan 340 ortopedik hastada LWMH'ne bağlı trombositopeni gelişimi retrospektif olarak değerlendirildi. Hastaların sadece %1.2'sinde (4/340) HIT ve bunlardan da sadece birinde femoral ven trombozu gelişti. Dört hastada da LWMH kesildikten sonra trombosit sayısı düzeldi. Sonuç olarak, HIT, LWMH tedavisinin sadece yaygın görülen değil aynı zamanda yüksek morbidite ve mortalitesi olan ciddi bir komplikasyonudur. Ayrıca sadece intravenöz/ciltaltı UFH kullanımı ile değil LWMH tedavisinde de görülebilir. Klinisyenler heparin tedavisi alan hastalarda trombositopeni ve tromboz komplikasyonlarına karşı dikkatli olmalıdırlar.

Anahtar Kelimeler: Düşük moleküler ağırlıklı heparinler, Trombositopeni, Ortopedik hastalar

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is the most important and most frequent drug-induced and immun mediated thrombocytopenia in patients receiving heparin, and has significant morbidity and mortality. HIT is an immune response in which the principal antigen is a complex of heparin and platelet factor 4 (PF4). PF4 is a positively charged molecule in granules of platelets which is released into the circulation and binds to the platelet surface when platelets are activated. Because of opposite charges, heparin and other glycosaminoglycans bind to the PF4 molecules that act as immunogens leading to antibody production. An IgG antibody is produced against the heparin-PF4 complex, and it binds to the complex which is on platelet surface and then the HIT antibody binds to the platelet and this interaction triggers activation and aggregation of the platelets. This platelet activation triggers to the production of prothrombotic platelet microparticles which promote coagulation. Finally, the HIT antibody-PF4-heparan sulfate complexes which is formed on the endothelial surface may induce tissue factor expression with further activation of the coagulation cascade and thrombin generation (1).

Thrombocytopenia in HIT is generally due to the clearance of activated and antibody-coated platelets by the reticulo-endothelial system (2). Typically, decreasing of platelet count begins 5 to 10 days after starting heparin, although a rapid decrase of platelet count may be seen in a patient who has antibodies from previous heparin use (3). Two different types of HIT are known. The first, HIT type I which is called non-immune heparin associated thrombocytopenia and has no increased risk of thrombosis. The mechanism of HIT type I is still unknown and this form effects up to 10 % of patients under heparin treatment which is characterized by a mild, transient and asymptomatic thrombocytopenia (rarely less than $100x10^9$/L) that develops early (usually within the first two days) and recovery is seen in short time after cessation of heparin. The second form of HIT, HIT type II, which is called as HIT is an immune-mediated reaction and associated with a high risk of thrombosis (4). Many studies suggest that up to 8 % of heparinized patients develops the HIT antibodies, approximately 1-5 % develops HIT with thrombocytopenia, and at least one-third of cases develops thrombosis (5-9). Generally, HIT antibodies occur more frequently in cardiovascular surgery patients than those undergoing orthopedic surgery, and in post-surgical patients than in medical patients. In addition, these antibodies are also more frequent in patients receiving unfractionated heparin (UFH) than in those treated with low molecular weight heparin (LMWH) (10,11). It must be underscored that antibodies developing in patients who treated

with UFH frequently cross-react with LMWH (8). We aimed to evaluate the effect of LMWH on developing HIT and thrombosis in orthopedic patients.

MATERIALS AND METHODS

The medical records of 468 patients who were hospitalized and had elective surgical procedure and complicated with thrombocytopenia during administration of LMWH in Orthopedics clinic of Dicle University Hospital in Turkey between January 2000 and November 2004 were evaluated retrospectively. Nadroparin calcium (Fraxiparine 0.3, 0.4, 0.6ml, GlaxoSmithKlein, Sweden) was administered subcutaneously for prophylaxis of thromboembolic complications 12 hours before and 12 hours after elective operation for 15 days. Thrombocytopenia was defined as a drop of > 50 % in the patient's platelet count from its baseline or a decrease in platelet count to below 100 x 10^9/L during the heparin therapy. Because of unavaliability to laboratuary conditions heparin-PF4 antibodies could not established and the diagnosis of HIT was determined clinically in the patients by the combination of the following features: 1- the occurrence of thrombocytopenia at least 5 days after beginning of heparin therapy, 2- the absence of any other clinical explanation for thrombocytopenia, and 3- the recovery of the platelet count after heparin cessation or the sudden death because of an unexpected thromboembolic event (2). After thrombocytopenia was seen in patients all the conditions potentially responsible for nonimmune thrombocytopenia were researched, and teh exclusion criteria were determined as following; recent heparin administration, an abnormal platelet count at baseline, an oncohematologic disease, sepsis, liver cirrhosis, disseminated intravascular coagulation, hemodilution from fluids/blood, concomitant chemotherapy, warfarin administration, and the remains were enrolled to the study. The clinical suspicion of thromboembolism was confirmed by the following methods: bilateral deep vein dupplex-ultrasonography in suspicion of deep vein thrombosis, ventilation/perfusion lung scintgraphy for pulmonary embolism, electrocardiography and enzymatic tests for myocardial infarction, and cerebral computarized tomography and cranial magnetic ressonance imaging in suspicion of stroke.

RESULTS

Of 468 eligible patients, 128 (27.3 %) were excluded because of recent heparin administration (n: 46, 35.9%), an abnormal platelet count at baseline (n: 31, 24.2%), an oncohematologic disease (n: 18, 14.1%), sepsis (n: 13, 10.1%), liver cirrhosis (n: 7, 5.5%), disseminated intravascular coagulation (n: 5, 3.9%), hemodilution from fluids/ blood (n:3, 2.3%), concomitant chemotherapy (n: 3, 2.3%), warfarin administration (n: 2, 1.6%). One hundred and ninety five of 340 patients (57.3 %) who were enrolled to the study were male and 145 (42.7 %) were female. The median age was 55 years (range 42-72). Of 340 included 4 patients' (1.2 %) platelet count dropped more than 50% from its baseline and lower than 100 x 10^9/L during the heparin teraphy and were accepted as HIT. The features of cases with HIT is shown in Table 1.

One of the patients (25 % of patients with HIT) had clinic findings of deep vein thrombosis. The deep vein thrombosis in the femoral vein was confirmed by duplex ultrasonography. After decreasing of platelet count the LMWHs therapy was discontinued and the patients were followed-up without any treatment. Platelet count were elevated spontaneously within several days (range 5-12). No major thromboembolic complication such as pulmoner thromboembolism or earlier patient's death due to an unexpected thromboembolic complication was seen.

DISCUSSION

Heparin is a drug that is widely used for prophylaxis of thrombosis or treatment in many clinical situations, including orthopedic and cardiac surgical procedures, acute coronary syndromes, cardiac arrythmias, venous thrombosis, peripheral occlusive diseases, and in dialysis during extracorporeal circulation (2,12). Administration of heparin may cause serious immune mediated adverse effects, including HIT which is a frequent, serious and potentially life-threatening complication if unrecognized (13-16). Because thrombocytopenia in hospitalized patients is a common and has variety of causative factors it is difficult to recognise HIT.

Table 1. Demographic and clinical features of patients with HIT

Patients with HIT	1	2	3	4
Age (years)	56	63	45	43
Gender (male/female)	Female	Female	Male	Female
Operation cause	Femur fracture	Femur fracture	Humerusfracture	Tibia fracture
LMWH dosage (ml)	0.6	0.3	0.3	0.4
Baseline Plt count ($x10^9$/L)	265	342	254	432
Dropped Plt count ($x10^9$/L)	40	55	35	45
Latest Plt count ($x10^9$/L)	344	232	187	452
Day of HIT occuring (days)	6	7	9	13
Day of recovery (days)	12	9	5	7
Thrombosis	(-)	(+)	(-)	(-)
Treatment	No	No	No	No

HIT is defined as a decrease in platelet count during or following exposure to heparin. It refers as a drop of >50% in the patient's platelet count from its baseline or a decrease in platelet count to below 100 x 10^9/L during the heparin teraphy (17). In recent study we found 4 cases of HIT in 340 patients (1.2%), and platelet count of all patients were below 100 x 10^9/L. When compared with literature although having lower incidence of HIT in our patients, 25% of patients with HIT developed thrombosis as it was similar to rates of literature.

In Type II HIT, the decrease in platelets usually occurs between 5 and 10 days after beginning of heparin, but its onset can occur earlier if there has been prior exposure to heparin (18). The earliest HIT case was occured on the sixth day of therapy and the latest one on the 13th day of the therapy. Thus an onset after than 10 days may not rule out the diagnosis of HIT. Not only thrombocytopenia the onset of a new thrombosis or extension of a preexisting thrombosis should further strengthen the clinical suspicion of HIT. Although criterion is not applicable at the onset of thrombocytopenia, it is helpful subsequently for confirmation of the diagnosis (19).

The diagnosis of HIT requires a fall in the platelet count during or soon after heparin therapy and objective confirmation of a heparin-PF4 dependent antibody. Two different types of assays are generally used for the detection of antibodies against PF4. The first assay is the enzyme-linked immunosorbent assay (ELISA), in which antibodies are detected immunologically and is more sensitive, second is the functional test detects antibody that is at a sufficient concentration to induce serotonin release from activated platelets or to induce aggregation of platelets from a healthy donor in the presence of patient serum and low concentrations of heparin (3). We could not determine the presence of HIT antibody because of unavailability to laboratuary conditions, so we diagnosed our patients with clinical findings and eleminating the other causes of thrombocytopenia. Recovery with cessation of heparin approved our diagnoses.

In a study Warkentin et al reported that the patients who have undergone orthopedic procedures were at high risk for developing HIT. In this prospective study of postoperative patients who received unfractionated porcine heparin the percent of developing HIT antibodies assessed by the antigen and functional assays was 14% and 9%, respectively; however, only 5% of the patients developed

thrombocytopenia (20). Other studies suggest these percentages as 8% for developing antibodies, 1-5% for developing thrombocytopenia and at least one-third of these patients suffer from thrombosis. In another study Warkenitin et al reported that HIT occurred in 9 of 332 (2.7%) patients who received UFH and in none of 333 patients who received LMWH (5). We found the ratio of HIT according to LMWH as 1.2 % in recent study and once more it must be highlighted that these reactions may occur by LMWH although it is less frequent than UFH and the clinicians must be aware of that this life threatening complication.

In HIT, thrombocytopenia is typically moderate in severity , but in only 10% of patients platelet count is less than 20 x 10^9/L and at least 10% of patients' platelet count never drops below 150 x 10^9/L. Despite low thrombocyte count, bleeding is uncommon in these patients (12), and HIT is strongly related to thrombosis, which leads to the recognition (21). Thrombosis in HIT is associated with a mortality rate of approximately 20-30%, with an similar percentage of amputation, stroke or other causes of permanent handicaps (22). Thromboembolic events may be arterial, venous, or both and include deep vein thrombosis, occlusion of major limb arteries, pulmonary thrombo-embolism, stroke and myocardial infarction (23). Even acute or chronic adrenal failure from bilateral adrenal hemorrhagic necrosis has been described (24). Warkentin et al reported that the incidence of deep vein thrombosis in orthopedic patients who received heparin for thromboprophylaxis as 17.8 %, but that this incidence increased dramatically to 88.9 % among patients who developed HIT (5). In recent study we found one-fourth of patients with HIT developed deep venous thrombosis (femoral vein thrombosis). In recent study none of patients died because of thrombotic event.

Treatment should not be delayed when HIT is suspected clinically. All forms of heparin must be discontinued immediatly, although this will neither stop continuing thrombin generation nor stop subclinical thrombotic events (25). In a retrospective analysis of 113 patients developed HIT, Wallis et al reported that early heparin cessation (0.7 ± 0.6 days) was not more effective in reducing morbidity and mortality than late heparin cessation (5 ± 3 days), thus only cessation of heparin is not adequate treatment for HIT (26). The appropriate treatment for HIT requires removal of the trigger immediatly by cessation of heparin as well as control of the thrombin generation by procuring alternative anticoagulation. In recent time, three non-heparin anticoagulants which do not cross-react with HIT antibodies, argatroban, lepirudin, and danaparoid are available for alternative anticoagulation in HIT (19,27-32). These drugs are immediately active and either inhibit thrombin directly or inhibit thrombin generation. HIT patients who are switched to warfarin after the cessation of heparin may paradoxically have worsening thrombosis and develop limb gangrene and necrosis (33). The mechanism seems to be a warfarin-induced marked decrease in protein C before prothrombin levels are adequately suppressed (12). We treated our patients by cessation of LMWH and follow-up without any anticoagulant because of inavaliability of alternative drugs, and all of the patients' platelet count came to normal levels between 6-13 days after cessation of heparin. One patients developed deep vein thrombosis but not major complication then. These results show us that cessation trigger immediately, UFH or LMWH, is still the most important point of treatment.

In conclusion, HIT is not only a common but also a serious complication of heparin therapy with a high rate of morbidity and mortality. In addition it does not seen only by intravenous/subcutaneous UFH but also by subcutaneous LMWH therapy. The clinicians particularly surgeons must be aware of occuring of this syndrome in their heparin receiving patients.

REFERENCES

1. Massimon F. Heparin-induced thrombocytopenia: an update. Thrombosis Journal 3:14, 2005.
2. Chong BH. Heparin-induced thrombocytopenia. J Thromb Haemost 1: 1471-1478, 2003.
3. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med 344: 1286–1292, 2001.
4. Rice L. Heparin-induced thrombocytopenia: myths and misconceptions (that will cause trouble for you and your patient). Arch Intern Med 164: 1961-1964, 2004.

5. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 332: 1330-1335, 1995.
6. Kelton JG. Heparin-induced thrombocytopenia: an overview. Blood Rev 16: 77-80, 2002.
7. Baglin TP. Heparin-induced thrombocytopenia/ thrombosis syndrome (HIT): diagnosis and treatment. Platelets 8: 72-82, 1997.
8. Comunale ME, van Cott EM. Heparin-induced thrombocytopenia. Int Anesthesiol Clin 42: 27-43, 2004.
9. Nand S, Wong W, Yuen B, et al. Heparin-induced thrombocytopenia with thrombosis: incidence, analysis of risk factors, and clinical outcomes in 108 consecutive patients treated at a single institution. Am J Hematol 56: 12-16, 1997.
10. Lindhoff-Last E, Eichler P, Stein M, et al. A prospective study on the incidence and clinical relevance of heparin-induced antibodies in patients after vascular surgery. Thromb Res 97: 387-393, 2000.
11. Locke CF, Dooley J, Gerber J. Rates of clinically apparent heparin-induced thrombocytopenia for unfractionated heparin vs. low molecular weight heparin in non-surgical patients are low and similar. Thromb J 3(1): 4, 2005.
12. Jang I-K, Hursting HJ. When heparins promote thrombosis. Review of heparin-induced thrombocytopenia. Circulation 111: 2671-2683, 2005.
13. Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. Br J Haematol 121: 535-555, 2003.
14. Warkentin TE. Heparin-induced thrombocytopenia. Diagnosis and management. Circulation 110:454-458, 2004.
15. Cines DB, Bussel JB, McMillan RB, et al. Congenital and acquired thrombocytopenia. Hematology (Am Soc Hematol Educ Program) 390-406, 2004.
16. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126(3 Suppl):311S-337S, 2004.
17. Warketin TE, Chong BH, Greinacher A. Heparin induced thrombocytopenia: towards consensus. Thromb Haemostas 79: 1-7, 1998.
18. Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. Heparin-Induced Thrombocytopenia, 1st ed. New York: Marcel Dekker. 2000: 43–80.
19. Chong BH. Diagnosis, treatment and pathophysiology of immune-mediated thrombocytopenia. Crit Rev Oncol Hematol 20: 271-96, 1995.
20. Warkentin TE, Sheppard JI, Horsewood P, et al. Impact of the patient population on the risk for heparin-induced thrombocytopenia. Blood 96: 1703-1708, 2000.
21. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med 101: 502-507, 1996.
22. Greinacher A. Antigen generation in heparin-associated thrombocytopenia: the nonimmunologic type and the immunologic type are closely linked in their pathogenesis. Semin Thromb Hemost 21: 106-116, 1995.
23. Warkentin TE. Heparin-induced thrombocytopenia: a clinicopathologic syndrome. Thromb Haemost 82: 439-447, 1999.
24. Warkentin TE. Clinical presentation of heparin-induced thrombocytopenia. Semin Hematol 35 (Suppl. 5) 9-16, 1998.
25. Alving BM: How I treat heparin-induced thrombocytopenia and thrombosis.Blood 101:31-37, 2003.
26. Wallis DE, Workman DL, Lewis BE, et al. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. Am J Med 106: 629-635, 1999.
27. Magnani HN. Heparin-induced thrombocytopenia (HIT): an overview of 230 patients treated with orgaran (Org 10172). Thromb Haemost 70: 554-561, 1993.
28. Greinacher A, Janssens U, Berg G, et al. Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. Heparin-Associated Thrombocytopenia Study (HAT) investigators. Circulation 1999, 100: 587-593.
29. Greinacher A, Volpel H, Janssens U, et al. Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. Circulation 99: 73-80, 1999.
30. Greinacher A, Eichler P, Lubenow N, et al. Heparin-induced thrombocytopenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of parenteral treatment with lepirudin and its therapeutic aPTT range. Blood 96: 846-851, 2000.
31. Lewis BE, Wallis DE, Berkowitz SD, for the ARG-911 Study Investigators. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 103: 1838-1843, 2001.

32. Chong BH, Gallus AS, Cade JF, for the Australian HIT Study Group. Prospective randomised open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopaenia with thrombosis: a clinical outcome study. Thromb Haemost 86: 1170-1175, 2001.
33. Warkentin TE, Elavathil LJ, Hayward CP, et al. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. Ann Intern Med 127: 804-812, 1997.

Correspondence
Dr. Dede Şit
Dicle Üniversitesi Tıp Fakültesi
Nefroloji Bölümü
21280, DİYARBAKIR

Tel/Fax: (+90) 412. 248 81 71
e-mail: drdede75@hotmail.com