LITERATURE REVIEW/CASE REPORT

Heparin-Induced Thrombocytopenia and Thrombosis Syndrome or H.I.T.T.S.

ALBERT H. OLIVENCIA - YURVATI, D.O., STEVE P. SANDERS, D.O., ERNEST PICKERING, D.O., ROBERT L. ARCHER, D.O.

Departments of Cardiovascular Thoracic Surgery and Internal Medicine
Oklahoma Osteopathic Hospital
Tulsa, OK

Key words: H.I.T.T. Syndrome, Heparin, Thrombocytopenia, Thrombosis

Abstract

Heparin induced thrombocytopenia has been reported to occur in 10-30% of patients receiving heparin therapy. Approximately 0.6-10% of these patients wlll develop a rare and poorly recognized paradoxical thrombosis. The suspected mechanism is an IgG mediated immune complex that causes platelet aggregation. Clinical hallmarks include thrombocytopenia, increasing heparin tolerance and recurrent arterial embolism. Laboratory testing as well as treatment modalities are presented. This paper reports on two open-heart surgery cases that developed heparin induced thrombocytopenia and the thrombosis syndrome (H.I.T.T.S.).

Introduction

Heparin was first introduced in 1916 by McLean, however, the anticoagulant properties were not used in clinical medicine until the 1960's. Heparin is derived from bovine lung and procine intestines, and is a large polar molecule that does not cross the placenta, nor is it orally absorbed. Heparin is quantified on a unit basis where one U.S.P. unit is equal to the quantity of heparin that will prevent 1.0 ml of sheep plasma from clotting for one hour after the addition of $CaCl_2$.[1]

Mechanism of Action

Thirty-three years after heparin was discovered (1949), physicians reported that heparin had no effect on platelets nor caused thrombocytopenia.[2] We now have documentation as to the mechanism of heparin anticoagulation as well as platelet aberrations. Heparin reversibly binds to antithrombin III, which causes a conformational change in the heparin molecule. This complex irreversibly binds to factors IIa, IXa, Xa, and XIIa, and therefore inactivates the clotting mechanism. Heparin will catalyze the inactivation of thrombin at high concentrations. In the absence of antithrombin III, heparin will inhibit the activation of prothrombin by factor Xa.[3]

Address correspondence to: Steve P. Sanders, D.O., 5501 East 48th Place, Tulsa, OK 74135

Heparin induced thrombocytopenia

Atkinson, et al. describes the mechanism of action of heparin associated thrombocytopenia.[4] These characteristics can be divided into four distinct types (**Figure 1**). Type 1: Acute-onset thrombocytopenia occurs immediately after the intravenous administration of heparin and is due to platelet clumping. The exact mechanism is not known. Type 2: Early-onset thrombocytopenia can be noted by the decrease in platelet counts approximately 2-4 days after the initiation of heparin, usually via the intravenous route. The mechanism may be due to an enhancement of the platelet-release phase of aggregation in response to ADP or epinephrine. This differs from a drug-induced thrombocytopenia because no platelet-associated antibody has been detected. Interestingly, this thrombocytopenia may resolve even with continuous heparin administration or rechallenge. Type 3: Delayed-onset thrombocytopenia (which is the focus of this paper) occurs 6-14 days after exposure or sooner in rechallenged patients. The occurrence has been noted despite route or dose. This is possibly an immunological mechanism with an IgM or lgG antibody, which has specificity for platelets. Type 4: Continued thrombocytopenia has components of direct heparin effects as well as antibody-mediated effects.

Figure 1

Classification of thrombocytopenia	Components
Type I Acute-Onset Thrombocytopenia	Direct effect on platelets
Type II Early-Onset	Platelet-release phase aggregations
Type III Delayed-Onset Thrombocytopenia	lgG mediated
Type IV Combined-Onset Thrombocytopenia	Mixed

Heparin induced thromboembolism

The first reported case of heparin-induced embolism occurred in 1958. Weismann and Tobin reported on 10 cases over a three-year period referring to the "white clot syndrome." In their study the period of heparin administration lasted 7-15 days, with a mean of 10 days. Six patients in this study died.[5] In 1966, Barker, Rosato, and Roberts reported the first large series to evaluate the causes of arterial embolism. Of the 110 patients treated for peripheral arterial embolism, heparin was implicated in 12% (13) of the patients treated.[6]

Pathogenesis

An early case report from Curry, et al. (1973) at the University of Oregon indicated that heparin sensitivity may result from an anaphylactic reaction to the drug.[7] Their patient's sera reacted in immunodiffusion studies with bovine lung but not porcine intestinal heparin. They suggested that the sensitivity resulted from an accelerated type 3 immune complex reaction to bovine heparin. A similar report of erythema and induration, secondary to 1.M heparin, also suggested a possible arthus reaction.[8] Another explanation of the local reaction of I.M. heparin implicates local platelet aggregation, with subsequent thrombosis in the vessels surrounding the injection site.[9]

Heparin induced platelet aggregation

A proposed immunologic basis for the development of the heparin-induced thrombocytopenia thrombosis syndrome (H.I.T.T.S) came from Duke University in 1973. The patients in this series were receiving both bovine and porcine heparin and underwent heparin rechallenge. The patients demonstrated clinical features that would later lead to four diagnostic hallmarks: (1) thrombocytopenia (2) megakaryocytosls (3) increased in-vitro platelet aggregation and (4) increasing heparin tolerance.[10]

Atkinson et al. suggested that heparin may have combined with platelet membranes and caused their subsequent removal from the circulation. Accelerated in-vivo platelet destruction may also have occurred and reduced the effect of heparin through platelet factor 4 release. Finally, increased platelet aggregation may accelerate in-vivo thrombosis, which would increase the quantity of thrombin available to neutralize heparin.

Clinical Sequela

The clinical spectrum of H.I.T.T.S. complications are varied. Asymptomatic to thrombotic events have been reported. Thrombotic events include pulmonary embolism, DVT, M.I., and digital vasculitis. Hematologic complications have also been reported from simple epistaxis to cerebral hemorrhage.[11] Laster et al. compared two series from 1983 and 1986, and noted a decrease in the incidence of H.I.T.T.S. associated thrombosis, possibly secondary to increased awareness of the syndrome. The majority of their patients who exhibited H.I.T.T.S. required thrombectomies, often followed by amputations.[12]

Incidence

A study done by Bell,et al. (1976) demonstrated a 30% incidence of thrombocytopenia occurring with heparin use.[13] All of the patients in this study were treated with bovine lung heparin. The patients had been on continuous heparin use for at least five consecutive days. Ten of 16 patients in this series developed elevated titers of fibrin degradation products. The investigators did not find a correlation between the lot numbers of the heparin used and subsequent thrombocytopenia. The thrombocytopenia appeared to be unrelated to the dose of heparin used. Later studies have shown that 82% of the patients who develop H.I.T.T.S. without serious complications, were on low dose therapy. However, 52% of patients wlth H.I.T.T.S., who were on full dose therapy, developed slgnificant complications.[14]

Heterogeneity of heparin

A series of patients with heparin-induced thrombocytopenia were studied at Johns Hopkins in 1980.[15] The authors hypothesized that thrombocytopenia occurrence was more frequent with bovine than with porcine mucosa heparin. The authors speculated that bovine lung heparin (due to its degree of sulfation) has a greater anionic charge density than porcine intestinal-mucosa heparin, and contains a variety of molecular species that are of higher molecular weight than the heparin derived from intestinal mucosa. Molecules of bovine lung preparation have greater avidity for binding antithrombin 111 and are extremely potent in prolonging the activated PTT and whole blood clotting time. The bovine lung tissue is recognized to have a higher concentration of tissue thromboplastin than porcine intestinal mucosa and is reported to contain 20X more Von Willebrand factor than any other tissue in the body. Trowbridge et al., also noted that there were longer APTT reaction times for porcine heparin, as compared to bovine heparin.[16]

Diagnosis

The difficulty with the diagnosis of H.I.T.T.S. is that there is no "gold standard"available for laboratory investigation. Routine clotting parameters such as PT, PTT, fibrinogen, and fibrin degradation products can all be within normal limits. Increased complement lysis inhibition studies have demonstrated increased levels of platelet-bound immunoglobulin.[19] The majority of clinical studies have used platelet aggregometry in laboratory support of the diagnosis. Heparin sensitivity can be conferred to normal platelets in vitro following incubation of the platelets with serum or plasma from patients with heparin induced thrombocytopenia.[17] Some investigators have measured the levels of B-thromboglobulin and platelet factor 4. These are platelet specific proteins that are secreted from the a-granules during the release reaction induced by ADP, epinephrine, arachidonic acid,collagen,and thrombin. A normal level of B-thromboglobulin is good evidence that increased platelet activation is not occurring in vivo.[18]

Clinical Diagnosis

A combined approach of both clinical and laboratory features has been proposed as the best method of diagnosing this syndrome.[19] The clinical features consist of heparin therapy (I.V.,S.C., H.F.)for longer than 5-6 days (unless prior exposure to heparin has occurred),venous or arterial thrombo-emboli while on heparin, or hemorrhage while on heparin. The laboratory features consist of thrombocytopenia, heparin resistance,heparin dependent platelet aggregating factor in plasma, and return of platelets to normal after ceasing heparin. Phelan (1983) demonstrated that thrombocytopenia is not an absolute requirement.[20] There may be a compensatory megakaryocyte response to platelet destruction or an exhausted platelet defect.

Treatment

The current recommendation for the treatment of H.I.T.T.S. is based upon early prevention. First and foremost treatment is the discontinuation of all heparin. The mortality associated with H.I.T.T.S. may average from 12 to 23%.

Ideally, patients receiving heparin for the treatment of DVT prophylaxis should be started on coumadin simultaneously to lessen the duration of heparin exposure.

Other treatment protocols for H.I.T.T.S. have been met with varied success, and no clinical trials have been reported. Plasmapheresis has been ineffective, possibly due to the extravascular dissemination of the heparin-dependent platelet activation factor and the binding of this substance to platelet membranes. Aspirin may be utilized by irreversibly acetylating cyclooxygenase and therefore inhibiting thromboxane A2 and prostaglandin endoperoxide formation. These substances appear to play a major role in platelet activation. Varied results are noted, possibly due to alternate thromboxane independent pathways.[21]

Iloprost (ZK 36374) is a stable analog of prostacyclin and is a potent inhibitor of platelet function. This prostanold appears to prevent platelet aggregation by blocking the effects of adenosine diphosphate and epinephrine. This to successfully treat the thrombotic complications of H.I.T.T.S.[23]

Due to a deteriorating clinical condition, the patient was placed on an intra-aortic balloon assist device and was taken to surgery for a two-vessel bypass and replacement of the mitral valve with a Carpentier-Edwards prosthesis. Four days later, a cyanotic appearance in the fingers and toes were noted. Thrombocytopenla was evident on laboratory investigation. All non-essential medications, including heparin, were discontinued to eliminate the possibility of drug-induced thrombocytopenia. No evidence of sepsis was found on serial blood cultures and an echocardiogram revealed no evidence of clots or masses on the mitral valve. The cyanosis was suspected to be an acute arterial embolization of unknown etiology. The patient was rebolused with 5,000 units of heparin and started on a continuous heparin infusion of 1,000 units/hr. Within 12 hours the patient's platelet count had fallen to 25,000. When the cyanosis of the lower extremities worsened the next day a clinical suspicion of H.I.T.T.S. was made. Heparin was stopped and the patient was started on oral coumadin therapy. Over the ensuing few days the cyanosis of the lower extremities demarcated and gangrene was evident. The patients platelet count began to rise to normal limits over the next two days. The patient subsequently underwent a Syme amputation of the right lower extremity and a below the knee amputation of the left lower extremlty.

Case #2 - The patient was a 50-year-old white male admitted through the emergency department after complaints of severe chest pain. The patient denied any previous history of angina pectoris or heart disease although he did have a long standing hlstory of hypertension. An ECG revealed evidence of an acute anterior wall myocardial infarction. The patient was given thrombolytic therapy (t-PA) shortly after admission followed by full dose heparinization. The patient improved and subsequently underwent coronary catheterization which revealed complete obstruction of the left anterior descending, high grade obstruction in the distal right coronary artery and high grade obstruction in the left circumflex. Also noted was akinesis of the anterior wall. During the cardiac catheterization the patient developed more chest pain and ST segment changes in the anterior leads. The patient was immediately taken to cardiac surgery and underwent three vessel coronary artery bypass grafting. The post-operative course was complicated by the development of congestive heart failure. The patient improved over the next three days and most medications, including heparin, were discontinued.

While recovering the patient developed possible thrombophlebitis of the left leg and again was placed on full dose heparin therapy. He subsequently developed a necrotic area in the distal incision of the saphenous vein graft and developed cyanosis and gangrene of the left foot, especially the fifth toe. He developed thrombocytopenia to a level of 15,000 platelets. H.I.T.T.S. was suspected and heparin was immediately discontinued. The patient was placed on oral coumadin therapy. The patient's platelet count subsequently returned to normal over the next five days. The patient was discharged and received outpatient whirlpool therapy with slow resolution of the necrotic areas. No surgical intervention was required due to the fast intervention.

Conclusions

Heparin-induced thrombocytopenia has been reported to occur in a low percentage of patients on heparin. Typically, this is transient and inconsequential to the patient. H.I.T.T.S., however, is a life threatening complication of heparin therapy. Two recent case reports of H.I.T.T.S. at our institution increased our awareness of this syndrome. Its diagnosis must be based on clinical suspicion and vigilant observation of platelet counts on any patient requiring heparin therapy. Platelet aggregometry, if available, should be performed to establish the presence of a heparin induced, IgG mediated, immune complex. Acute intervention consists of immediate discontinuation of heparin and use of alternative forms of anticoagulation.

References

1. O'Reilly, RA.: Anticoagulant, antithrombotic, and

thrombolytic drugs. Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. AG Gilman, LS Goodman, A Gllman (eds), New York: Macmillan Publishing Co, 1980, p. 1348- 1353.

2. Quick, AJ, Shanberge, JN, Stefanini,M.: The effect of heparin on platelets in vivo. *J. Lab. Clin. Med.* 33: 1424-1430, 1948.

3. Hirsh, J, Ofosu, F, Buchanan, M.: Rationale behind the development of low molecular weight heparin derivatives. *Semin. Thromb. Hemost.* II: 13-16, 1985.

4. Atkinson, JLD, Sundt, TM Jr., Kazmier, FJ, et al.: heparin-induced thrombocytopenia and thrombosis in ischemic stroke. *Mayo Clin. Proc.* 63: 353-361, 1988.

5. Weismann, RE, Tobin, RW: Arterial embolism occurring during systemic heparin therapy. *A.M.A. Arch. Surg.* 76. 219-227, 1958.

6. Barker, CF, Rosato, FE, Roberts, B: Peripheral arterial embolism. *Surg. Gyne. Obstet.* 7: 22-26, 1966.

7. Curry, N, Bardana, EJ, Plrofsky, B: Heparin sensitivity. Report of a case. *Arch. Intern. Med.* 132: 744-745, 1973.

8. O'Toole, RD: Heparin: Adverse reaction. *Ann. Intern. Med.* 79: 759, 1973.

9. White, PW, Sadd, JR, Nensel, RE: Thrombotic complications of heparin therapy. *Ann. Surg.* 190: 595-608, 1979.

10. Rhodes, GR, Dixon, RH, Silver, D: Heparin induced thrombocytopenia with thrombotic and hemorrhagic manifestations. *Surg. Gyn. Obstet.* 136:409-416, 1973.

11. Arthur, CK, Isbister, JP, Aspery, EM.: The heparin induced thrombosis thrombocytopenia syndrome (H.I.T.T.S.): a review. *Pathology* 17: 82-86, 1985.

12. Laster, J, Cikrit, D, Walker, N, et al.: The heparin-induced thrombocytopenia syndrome: an update. *Surgery* 102: 763-770, 1987.

13. Bell, WR, Tomasulo, PA, Alving, BM, et al.: Thrombocytopenia occurring during the administration of heparin. *Ann. Intern. Med.* 85: 155-160, 1976.

14. Laster, J, Cikrit, D, Walker, N, et al.: The heparin-induced thrombocytopenia syndrome: an update. *Surgery* 102: 763-770, 1987.

15. Bell, WR, Royall, RM: Heparin-associated thrombocytopenia: a comparison of three heparin preparations. *N. Engl. J. Med.* 303: 902-907, 1980.

16. Trowbridge, AA, Caraveo, J, Green, JB 111, et al.: Heparin-related immune thrombocytopenia. *Am. J. Med.* 65: 277-283, 1978.

17. Kapsch, DN, Adelstein, EH, Rhodes, GR, et al.: Heparin-induced thrombocytopenia, thrombosis, and hemorrhage. *Surgery* 86: 148-155, 1977.

18. Kaplan, KL, Owen, J: Plasma levels of B-thromboglobulin and platelet factor as indices of platelet activation in vivo. *Blood* 57: 199-202, 1981.

19. Arthur, CK, Isbister, JP, Aspery, EM: The heparin induced thrombosis thrombocytopenia syndrome (H.I.T.T.S.): a review. *Pathology* 17: 82-86, 1985.

20. Phelan, BK: Heparin-associated thrombosis without thrombocytopenia. *Ann. Intern. Med.* 99: 637-638, 1983.

21. Kappa, JR, Fisher, CA, Berkowitz, HD, et al.: Heparin-induced platelet activation in sixteen surgical patients: Diagnosis and management. *J. Vasc. Surg* 5:101-109, 1987.

22. Addenizio, VP, Fisher, CA, Jenkin, BK, et al.: Iloprost (ZK36374), a stable analogue of prostacyclin, preserves platelets during simulated extracorporeal circulation. *J. Thorac. Cardiovasc. Surg.* 89: 926-933, 1985.

23. Clifton, GD, Smith, MD: Thrombolytic therapy in heparin-associated thrombocytopenia with thrombosls. *Clin. Pharm.* 5: 597-601, 1986.

24. Rizzoni, WE, Miller, K, Rick,M., et al.: Heparin-induced thrombocytopenia and thromboembolism in the post-operative period. *Surgery* 103: 470-476, 1988.