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Heparin Induced Thrombocytopenia

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ABSTRACT

Background: Heparin is a widely used anti-thrombotic agent for treatment of ischemic cerebrovascular disease. One of its most important side-effects is thrombocytopenia which may lead to potentially life-threatening haemorrhagic and thrombotic complications.

Methods: We performed a prospective study to determine the frequency of heparin induced thrombocytopenia. Heparin induced thrombocytopenia is defined as a platelet count of less than 150 x 10^3/mm^3 or a decrease in platelet count to 30% to 50% from baseline. Daily platelet counts were obtained in 50 adult patients who were treated with the same lot of intravenous bovine heparin. Two patients (4%) developed thrombocytopenia with onset varying from four to seven days after heparin was started. In both cases, platelet counts returned to baseline levels three to five days after cessation of therapy. No ischemic or haemorrhagic complications occurred.

Conclusion: Heparin induced thrombocytopenia is a common complication of intravenous heparin treatment. Clinicians treating patients with heparin should determine platelet counts at baseline and henceforth at regular intervals beginning from the fifth day of therapy. We recommend commencement of warfarin therapy concurrently with heparin infusion and discontinuation of heparin once warfarin has become effective. All doctors must be vigilant to this reversible common complication.

Keywords: heparin, thrombocytopenia, platelet, cardiovascular, stroke

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INTRODUCTION

Heparin has been used as an anti-thrombotic agent for more than 50 years[1,2]. One of its most important side effects is thrombocytopenia. The reported incidence varied from 1 to 31%[3-7]. Heparin induced thrombocytopenia (HIT) may lead to haemorrhagic and thrombotic complications which are potentially life threatening[8,9]. However HIT is underdiagnosed due to a lack of awareness by many doctors. In our institution, we treat many patients with ischemic cerebrovascular disease with heparin. Hence we decided to conduct a study on the incidence of HIT.

METHOD

This is a prospective study in Tan Tock Seng Hospital conducted over six months from July 1996 to December 1996. All patients with ischemic stroke who received intravenous heparin for a minimum of five days were included in the study. The diagnosis of ischemic stroke was established according to standard criteria[10]. Each patient was followed through the entire period of hospitalisation. All medications concurrently administered during the study period were noted, specifically cimetidine, thiazides and sulphonamides.

THERAPY

Continuous intravenous bovine heparin (B. Braun Melsungen AG, Germany) was initiated at a dose of 5000 units six hourly using an infusion pump. The goal of therapy was to achieve a PTT of 1.5 to 2 x control.

LABORATORY TESTS

Baseline haemoglobin, haematocrit, leucocyte count, platelet count, prothrombin time and thromboplastin time were obtained before starting heparin. Subsequently, they were monitored daily until therapy was discontinued. A coagulopathy screen comprising serum fibrinogen, D-dimers and soluble monomers was obtained if thrombocytopenia was accompanied by sepsis.

HEPARIN INDUCED THROMBOCYTOPENIA

The diagnosis of HIT is based on clinical criteria and platelet count and not on laboratory testing. Most authors define thrombocytopenia as a platelet count of less than 150 x 10^3/mm^3 or a decrease in platelet count to 30% to 50% from baseline[5,9,11-15]. There is no given

Table I. Characteristic features of patients with heparin induced thrombocytopenia

No.	Sex	Age	Diagnosis	Baseline Platelet count ($10^3/mm^3$)	Onset of thrombo-cytopenia (days)	Lowest platelet count ($10^3/mm^3$)	Day of lowest platelet count	% drop in platelet count	Days to recovery	Ischemic events	Outcome
1.	M	77	Crescendo TIAs	293	7	128	9	56	5	Nil	Improved
2.	F	82	Brainstem stroke	164	4	113	5	31	3	Nil	Improved

platelet count at which a diagnosis of HIT can be made. Other potential causes of thrombocytopenia like disseminated intravascular coagulopathy must be excluded.

RESULTS

Fifty adult patients with age ranging from 31 to 82 years (median 58) were studied. Thirty had cerebral infarcts, 14 had brainstem infarcts and six had transient ischemic attacks (TIAs). They were anticoagulated with intravenous heparin for 8 $\pm$ 2.5 days.

All patients had a baseline platelet count more than 150 x $10^3/mm^3$. Two patients (4%) developed heparin-induced thrombocytopenia (Table I). The onset of thrombocytopenia ranged from four to seven days after heparin was started, with a corresponding decrease in platelet count from 31 to 56%. Platelet counts returned to normal range three to five days after cessation of heparin therapy. There were no ischemic events and all patients survived.

In 36 patients (72%), the platelet count decreased from 8 to 24% of baseline values between days 1 to 5 of heparin therapy (mean 2 $\pm$ 1.5). Anticoagulation was continued and platelet counts normalised within 2 to 5 days (mean 3 $\pm$ 1.5). These patients did not have any haemorrhagic or thrombotic events.

DISCUSSION

HIT is a common complication of patients treated with intravenous heparin therapy, occurring in 4% of patients who received this drug. We conclude that the fall in platelet count is due to heparin therapy because of the following reasons: firstly, platelet counts fell progressively during anticoagulation and returned to baseline levels after heparin was discontinued. Secondly, these patients were not receiving any drugs which might cause thrombocytopenia like thiazides, cimetidine and sulphonamides. Thirdly, all patients were well and not in disseminated intravascular coagulopathy.

A literature survey revealed that the incidence of HIT varied widely among different authors. This is due to several variables that exist between studies, of which the most important is the definition of thrombocytopenia. Whereas some used a platelet cutoff level of 150 x $10^3/mm^3$ [5,9,11-15] others used 100 x $10^3/mm^3$ [6-8,16-19]. In addition, different types of heparin (bovine versus porcine) were used and each type came from a different lot. In our study, we resolved this problem by using only one lot of bovine heparin. The duration of heparin therapy and frequency of platelet count determination was not uniform among different investigators; it ranged from three to ten days. This is important because thrombocytopenia is typically delayed in onset (occurring five or more days after the start of heparin therapy) and HIT may not be detected in patients who are monitored for only a few days. Other variable factors include the route of heparin administration (continuous or intermittent intravenous infusion or subcutaneous), the dose of heparin used and the diluent and tubing used to administer heparin[18].

The pathogenesis of HIT may include heparin-dependent immunoglobulin G (IgG) antibodies that activate platelets through their Fc receptors, in the presence of small amounts of heparin[20,21]. Heparin may react with platelet factor 4 (PF4) which is normally present on the surface of endothelial cells or released from circulating platelets. A PF4-heparin complex is then formed which binds with specific IgG antibodies to form a PF4-heparin-IgG immune complex. This immune complex binds to the platelet Fc receptors, resulting in platelet activation, aggregation and subsequent platelet and endothelial cell destruction. The binding of PF4 with circulating heparin perpetuates the cycle of ongoing platelet activation and destruction. The PF4, especially when present in excess amounts that can complex with heparin, binds with heparin-like molecules on the surface of the endothelial cells (eg glycosaminoglycans). This binding can result in immune-mediated cell injury with an increased risk for thrombotic events and disseminated intravascular coagulopathy[8,9].

In addition to HIT, mild thrombocytopenia of early onset may occur after commencement of heparin infusion. This is due to an intrinsic pro-aggregatory effect of heparin and is a benign condition[9,15,18,22].

Clinicians treating patients with heparin should be aware of the risk of heparin-induced thrombocytopenia

and determine platelet counts at baseline, day 5 of therapy and at regular intervals henceforth.

Our approach to patients who require anticoagulation for ischemic cerebrovascular disease is to commence warfarin therapy concomitant with intravenous heparin infusion. Warfarin requires 48 to 72 hours to reach therapeutic levels. We maintain the patient on heparin for the minimum interval to allow warfarin to become effective. This strategy ensures expeditious anticoagulation while avoiding HIT, since HIT usually occurs seven to 14 days following exposure to heparin. Once HIT is diagnosed, heparin must be discontinued immediately[5,19,23]. If continued anticoagulation is required and warfarin treatment has not reached therapeutic levels, alternative antithrombotic agents may be used in the interim period. These include ancrod, dextran and heparinoids[8,9,24]. Unfortunately none had been proven to be uniformly effective.

CONCLUSION

HIT occurred in 4% of patients treated with intravenous heparin. No thrombotic or haemorrhagic complications occurred. In all cases platelet counts returned to baseline levels after cessation of heparin therapy. Clinicians treating patients with heparin should determine platelet counts at baseline and henceforth at regular intervals beginning from the fifth day of therapy. We recommend commencement of warfarin therapy concomitant with intravenous heparin and discontinuation of heparin once warfarin has become effective. All doctors must be vigilant to this reversible common complication.

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