ORIGINAL ARTICLE

Frequency of Heparin Induced Thrombocytopenia – a Single Centre Experience

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ABSTRACT

Heparin is an important and very commonly used anticoagulant. Its use is associated with many complications like hemorrhage, heparin induced thrombocytopenia (HIT), osteoporosis and alopecia. HIT carries a high mortality rate , however, it is often missed. Our objective was to determine the frequency of HIT during heparin therapy by any route. The study was conducted in cardiology, cardiac surgery and medical wards of Mayo hospital, Lahore, from JUNE 2009 to December 2009. Four hundred patients were included in the study. A detailed clinical history was recorded. The history was supported by relevant investigations. Heparin was administered by intravenous infusion after a loading dose or subcutaneously six hourly . Peripheral venous samples were taken in EDTA anticoagulant on alternate days for platelet count estimation. Platelet counts were performed on Sysmex KX 21 and compared with peripheral blood smear. Low platelet counts were confirmed mannualy on neubauer chamber**.** Out of 400 patients 14 patients developed HIT. The frequency was 3.5%. Patients should be closely monitored HIT to detect its onset.

Keywords: Thrombocytopenia, Heparin, Frequency

INTRODUCTION

Heparin is a drug widely used for thromboprophyaxis and treatment in many clinical situations [1]. It is a naturally occurring sulfated glycosaaminoglycan. It is normally present in many human tissues. McLean was the first person who isolated it from ox liver and later identified its anticoagulant properties[2]. Commercial unfractionated heparin which is now available is derived from bovine lung or porcine intestinal mucosa. The enzymatic cleavage of unfractionated heparin produces low molecular weight heparin.

Low molecular weight heparin has a smaller and more uniform size. It has limited antithrombin activity owing to its reduced number of pentasachride molecules.

The wide spread use of heparin in hospitals is unavoidable[3]. Almost one third of hospitalized patients receive heparin due to different clinical conditions. The wide spread use of heparin is unfortunately associated with certain complication. Hemorrhage is commonest of all. Others include heparin induced thrombocytopenia, osteoporosis and alopaecia[4].

Heparin induced thrombocytopenia (HIT) is a serious and potentially life threatening condition. It requires a high index of suspicion. Since thrombocytopenia is common in hospitalized patients and could be caused by a number of conditions, heparin induced thrombocytopenia often remains unrecognized[5].

Heparin induced thrombocytopenia (HIT) is suggested by decrease in platelet count during or shortly following heparin therapy by any route in the absence of other cause of thrombocytopenia [6] Other causes of thrombocytopenia include immune thrombocytopenia, megaloblastic anaemia, malaria, leukaemia, lymphoma, bone marrow infiltration, spleinc over activity and viral infections [7]. Thrombocytopenia or abnormal platelet function characterized by purpura, bleeding from mucous membrane or conversely by an episode of thrombosis during heparin therapy can be a sequel of HIT[8].

HIT is clinically divided into two types[9]. HIT Type I is more common than HIT type- II. HIT Type I is a trivial and clinically benign condition. It usually occurs early during heparin therapy. It is not associated with increased risk of thrombosis. It presents as fall in platelet count due to platelet agglutination. Thrombocytopenia is transient and asymptomatic. The platelet count rarely falls below 100,000/ul. Restoration of platelet count occurs quickly once heparin therapy is withdrawn. HIT Type II is seen in 1-3% of all the patients receiving heparin. It is an immune mediated response characterized by formation of autoantibodies against platelet factor 4/heparin complex[10]. It presents as moderate to severe condition manifesting as purpura to overt

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bleeding. Conversely, it may present as thrombosis of a major vessel.

HIT, Type II is a potentially fatal condition with mortality of about 30% [11]. It typically affects arterial circulation in patients of ischaemic heart disease or cerebrovascular accidents. Whereas, venous system is affected in patients of deep venous thrombosis. There is often evidence of extension of thrombosis despite adequate level of anticoagulation. Skin may show necrosis at site of injection if subcutaneous route is selected. Disseminated intravascular coagulation is most feared complication of Type II [12]. A more recent and advance test PF4-Elisa gives highly specific and sensitive results in patients treated with heparin [13]. Immediate discontinuation of heparin therapy is the rule whenever HIT is diagnosed.

Low molecular weight heparin has fairly low incidence of HIT [14]. It is safe and does not require constant monitoring unless bleeding is observed[15]. It produces desirable anticoagulation effects after first dose compared to unfractionated heparin which requires some dose adjustment[16]. Whenever, HIT is suspected anticoagulation can be continued with lepirudin (recombinant hirudin)and other substitutes like Argatroban or Ximelogatran can be cotinued[17]

OBJECTIVES

1. To determine the frequency of HIT during heparin therapy by any route.
2. To study other variables of HIT which include relationship with age, gender and time of onset.

MATERIAL AND METHODS

The study was conducted in all medical units, cardiology and cardiac surgery ward of Mayo Hospital Lahore, in patients admitted through outpatient and emergency departments, from June 2009 to December 2009. It is a descriptive type of study.Four hundred consecutive patients admitted in above mentioned wards were included in the study. Patients on unfractionated heparin therapy for anticoagulation and patients of adult age group (over 12 years), both male as well as female. were included in the study. Diagnosed case of megaloblastic anaemia, leukemia, multiple myeloma, myelofibois, solid tumors and metastasis, aplastic anaemia, paroxysmalnocturnal haemoglobinuria(PNH) and chronic myeloid leukemia were excluded.

After selecting the subjects of study, their socio-demographic information was obtained. A thorough and methodical clinical history was taken to rule out inherited bleeding and platelet disorders as well as all the acquired causes of thrombocytopenia and quantitative platelet disorders mentioned above. The patients included in the study were examined . The history and physical findings were supported by relevant investigation like peripheral blood picture, urine complete examination, estimation of serum urea and creatinine level, liver function tests ,c-reactive protein level and X-ray chest (if required). The date at which unfractionated heparin was administered was recorded. The route of administration, which was either a continuous I/V infusion after a loading dose or six hourly / twelve hourly subcutaneously route was recorded. Follow up of patients was performed on alternate days for seven days. Their peripheral venous blood samples were taken in ethylenediamine tetra-acetic acid (EDTA) anticoagulant on alternate days for the estimation of platelet count for one week. Platelet counts were performed on Sysmex Kx 21 blood auto analyzer and on blood smears. Low platelet counts were confirmed manually using improved neubauer chamber. Heparin induced thrombocytopnia was considered if platelet count decreased below 150,000/ul or >50 % of the base line platelet count. The first day of heparin therapy was recorded as day one. With that point of reference, the first day that the platelet count was shown to have fallen below 150,000/ul or > 50 % of baseline platelet count was assumed to be the day of HIT occurrence. The time interval between the initiation of heparin therapy and decrease in platelet count was identified as **"time of onset"** of heparin induced thrombocytopenia. Data was entered on and processed using statistical program for social sciences (SPSS) version10. T–test was applied as test of significance**.**

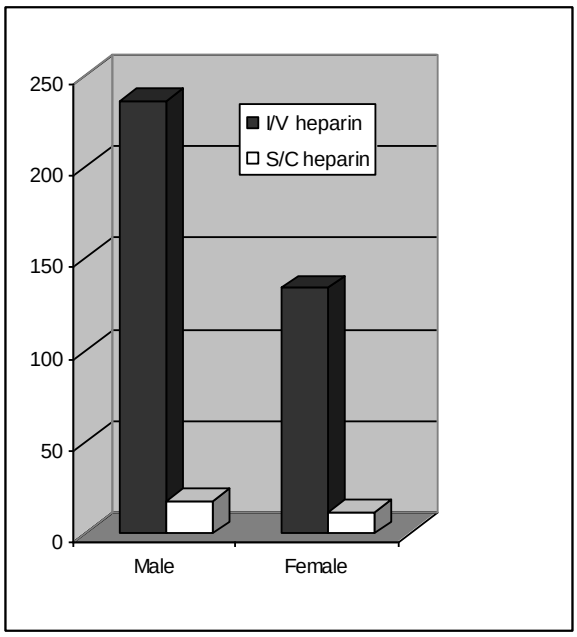
RESULTS

A total of four hundred adult patients were included in the study. Out of these 248 (62%) were males and 152 (38%) were females . The age of patients ranged from 19-95 years. The mean age was 52.4 years.

All the patients were given heparin therapy for their different diseases.370 (92.5%) were given intra venous heparin (236 males and 134 females). 30(7.5%) patients were given heparin by subcutaneous route (18 males and 12 females) (figure 1)

Antiplatelet therapy was prescribed to 370 patients. 218(58.9%) patients received aspirin (156 males and 62 females), while 62 (16.7%) patients were given clopidrogrel (30 males and 32 females). 86(23.2%) patients received both aspirin and clopidrogrel (46 males and 40 females). Four (1%) patients were given ticlopidine, all were female (Figure 2).

Figure 1 :Mode of Heparin Administration



Platelet count was performed of all the patients at initiation of heparin therapy and was marked as day one. 252 (63%) patients had platelet counts in the range of 150,000/ul-249,000/ul (164 males and 88 females). 140(35%) had their platelet count between 250,000/ul-349,000/ul (80 males and 60 females) and 8 (2%) had between 350,000/ul-450,000/ul (4 males and 4 females) (table 1).

Patients were followed up and platelet counts were performed on alternate days till day 7 .A decrease in platelet count below 150,000/ul was observed in 14 patients (3.5%), 8 patients were male and 6 females . In 8 patients platelet count was in the range of 101,000/ul-149,000/ul and in 6 patients it was between 50,000/ul-100,000/ul. The decrease in platelet count was found highly significant (p <0.001).(Table 1 & 2). In 12 patients platelet count decreased below 150,000/ul on day 7 and in 2 patients it decreased between day 1 and 3..

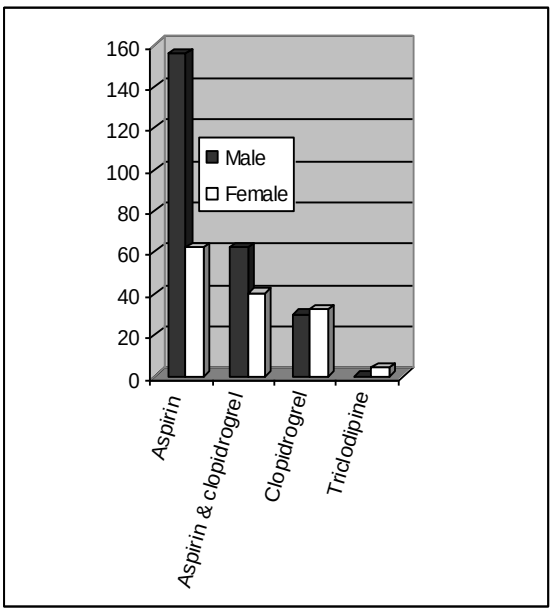
Table 1: Platelet Count On Day 1

Platelet count in UL/ML	**Male**	**Female**	**Total**
150,00/ul-249,000/ul	164	88	252
250,000/ul-349,000/ul	80	60	140
350,000/ul and above	04	04	08
Total	248	152	400

Table 2: Platelet Count On Day 7

Platelet count in ul/ml	**Males**	**Females**	**Total**
50,000/ul-100,000/ul	4	2	6
101,000/ul- 149,000/ul	4	4	8
150,000/ul-249,000/ul	158	88	246
250,000/ul-349,000/ul	78	56	134
350,000/ul and above	4	2	6
Total	248	152	400

Figure 2: Antiplatelet Therapy



DISCUSSION

Heparin is administered by different routes but the most common one is continuous intravenous infusion. The therapy is given for a number of days in different clinical situations. Thrombocytopenia is a dangerous complication observed during heparin therapy. Contrary to its name it is associated with thrombosis rather than hemorrhage. Thrombosis carries a morbidity and mortality rate of 66%[18].

Charles et al [19] stated that a drop in platelet count of 50% or more or platelet count less than 150,000/ul after initiation of heparin therapy is considered as a diagnostic criteria for HIT. Charles et al reanalyzed Warkentin data by the above mentioned definition and compared the rate of HIT in unfractionated heparin and low molecular weight heparin. HIT was more pronounced, being eight times greater in patients treated with unfractionated heparin than the low molecular weight heparin group (4.8% versus 0.6%). We used this criterion and cited the rate of HIT as 3.5%. His data was only from surgical patients receiving heparin for prophylaxis. Our data consisted of patients from medical and cardiology wards mostly (97.5%) having heparin for various prophylactic as well as therapeutic indications. We had 10 (2.5%) patients from cardiac surgery ward .The medical and cardiac surgical patients combined together showed 3.5% frequency of HIT. When Warkentin data was applied to non-surgical patients it showed frequency of 0.3%. Whereas our study revealed a frequency of 3.5% in mostly non-surgical patients. It can be said that given variation is due to lack of standardization in

diagnosis, hospital stay and less vigilant evaluation of patients for HIT. It was impossible to calculate the relative risk in the study done by Warkentin and Walenga et al, but showed that HIT is uncommon with unfractionated heparin and unlikely with low molecular weight heparin[15]. Same holds true for our study but we lack the data for low molecular weight heparin.

In the study done by Warkentin et al [6], it was found that HIT occurred regardless of factors like age and time of onset. In our study we found that age and time of onset of HIT are insignificant as relative risk in accordance to study by Warkentin et al.

In another study conducted by Warkentin et al [20] it was seen that HIT occurred more frequently in females as compared to males. In our study male preponderance was seen in patients of HIT.This could be due to lack of referral of female patients to tertiary care hospital.

In a recent study done by Girolmini et al it was stated that HIT is strongly associated with 10-21 days of heparin therapy[21]. This was consistent with college of American pathologists (CAP) 2002 [22] and American college of chest physicians [23]evidence-based clinical practice recommendations. In these it was emphasized to focus the attention on platelet count monitoring between day 4-10 of heparin therapy. College of American pathologists declared surgical patients as high risk and non surgical patients as intermediate risk patient for HIT. In our combined study for both surgical and non surgical patients a decrease in platelet count less than 150,000/lul was observed on day 7. Our study was confined to seven days after the initiation of heparin therapy. Moreover, in both these studies and our study no attention was focused on patients having repeated admissions. Repeated heparin therapy increases the chances of HIT. Due to various socio-economic problems, it is difficult to keep the patient in hospital for more than 5-7 days in our set up. Owing to this reason our study span could not be increased more than 7 days.

The diagnosis of HIT on the basis of decrease in platelet count alone should not be considered sufficient in an era of evidence based medicine. The gold standard test for diagnosis is 14-C serotinine release assay(1,2). Detection of antibodies against heparin-platelet factor 4(hepain-PF4) by Elisa is a newer technique[24]. Unfortunately no such technique is available in Pakistan. There is no routine testing for platelet counts in reference to HIT. The clinical suspicion arises when there is drop in platelet count in peripheral blood examination or thrombosis during or after heparin therapy. The need for this simple test should be emphasized because those who have HIT, have a 60-66% chance of developing fatal arterial or venous thrombosis leading to myocardial infarction, stroke or gangrene.

Girolami et al studied HIT specifically in medical patients on subcutaneous heparin therapy. This study included consecutive patients, out of which 5 developed HIT. Amongst them 3(60%) developed fatal thromboembolic complications (ischaemic stroke, myocardial infarction and lower limb arterial occlusion) either during administration of 598 heparin or soon after discontinuation of therapy[21]. The study showed incidence of HIT equal to that observed in patients on intravenous therapy. In our study 15 patients received heparin by subcutaneous route and only one patient developed HIT. Such high incidence in Girolami's study could be due to lack of standardization of patient's primary disease and its out come. But it should be noted that the incidence of HIT was consistent with that observed by Warkentin in non surgical patients.

Greinaher at al studied HIT and associated complications in 408 patients[25]. They like Girolami et al observed predominance of deep venous thrombosis (2.4:1), with 40% patients developing pulmonary embolism. However arterial thrombosis was common in patients of cardiovascular surgery. In 59.8% of patients HIT related thrombosis manifested either on the day of less than 50% platelet count decrease (26.3%) or before the decrease in platelet counts (33.5%). The most important risk factor for thrombosis was orthopaedic surgery. Study of Girolami at al and Greinacher et al implies the importance of HIT and associated thrombosis as a complication of routine heparine therapy. This can be an eye opener for clinicians advising unfractionated heparin therapy.

Mattioli at al followed up 124 patients for one year[26]. These patients were given unfractionated heparin. They observed that the patients who developed antibodies against heparin platelet factor 4 after 6 days of heparin therapy had morbidity and mortality of 66% due to myocardial infarction , stroke and unstable angina. Whereas in patients who did not develop antibodies it was 44%.Thrombotic episodes were more common in patients who received heparin again within one year. Nevertheless more accurate evaluation and surveillance was required in these patients after hospital discharge.

In our study patients were followed up from day1-7. Heparin was stopped in 2 patients due to haemoptysis and haematuria. Their platelet count remained normal. 7 patients developed thrombocytopenia. None of patients developed thrombotic complications. In our study 370 patients were on antiplatelet therapy. 218 were having aspirin, 62 had clopidrogrel and 86 had both clopidrogrel and aspirin both. 4 patients received ticlopidine.

Antiplatelet drugs are useful in preventing thrombosis. More studies should be carried out to ascertain the importance of these drugs in preventing thrombosis in patients of HIT. Since thrombosis is more likely in patients who develop antibodies against heparin platelet factor 4, development of antibody assay in our country would be of great help in detection and diagnosis of HIT. Moreover, we would be able to save more patients in follow up against high incdience of thrombosis.

In our local study, Naz R et al has compared the unfractionated heparin with low molecular weight heparin in patients with deep venous thrombosis[27]. They observed thomboemolic complications to be 4.5% amongst patients on unfractionated heparin. This is an indirect evidence of antibody mediated thromosis observed by foreign authors.

Chen et al showed that medication with unfractionated heparin was cheaper but its labatory test monitoring was expensive as compared to low molecular weight heparin, which was although expensive but did not require libratory monitoring [28] .Moreover its safety has made it possible to treat patients on out patient basis, thus further reducing the cost. The high efficacy and low side effects are another indication for its preference[25]. According to the American college of chest physicians guide lines, although the cost of low molecular weight heparin is more as compared to unfractionated heparin in America than in Europe, but its safety, efficacy and administration on out door basis will significantly reduce the total health care cost[23]. However sufficient data is currently not available and efforts should be made before reducing the use of unractionaed heparin.

We suggest a rigorous evaluation of HIT using definitions proposed by Dr. Warkentin in 2003, in future studies done for unfractionated as well as low molecular weight heparin in both surgical as well as non surgical patients [29].

CONCLUSION

Considering the wide spread use of heparin in a number of conditions both prophylactic as well as therapeutic, all the patients should have close clinical and laboratory surveillance for estimation of platelet counts to rule out HIT. An alternate preventive, prophylactic and therapeutic anticoagulant like liperudin or hirudin etc should be available at hand in case of HIT. Recommendations should be gathered by meta analysis for use of antiplatelet drugs with unfractionated heparin to avoid life threatening thrombosis in patients with HIT.

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