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Research Article

Heparin Induced Thrombocytopenia

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ABSTRACT

This is a prospective study to evaluate the incidence of Heparin induced thrombocytopenia (HIT) with its complications in-patients treated with intermittent intravenous heparin therapy. The study was done in al salam General Hospital in Mosul from 1/2/2022 to 31/8/2022.
Two hundred patients were treated with heparin sodium of porcine gut origin (Heparin Leo) in doses of (20,000 – 30,000 unit/day) by intermittent I.V. route for 4-10 days.
Platelet count was measured within 24 hours of the initiation of heparin therapy then on days 2, 4, 7, 11 and 14 thereafter with more frequent checking in those who developed significant reduction in platelet count.
HIT is divided into two types: HIT1 in which thrombocytopenia developed in the first four days of heparin therapy. (12) Cases (6%) were discovered, thrombocytopenia was mild-moderate in severity and no complications were observed and heparin therapy continued, and HIT2 in which thrombocytopenia developed after the 4th day of initiation of heparin therapy, (4) cases (2%) were observed with more severe form of thrombocytopenia and no thrombotic complications were observed.
Heparin induced thrombocytopenia is a common unnoticeable side effect of heparin therapy, it may have grave thrombotic complications which is usually associated with the reduction in platelet count, so we performed this study to evaluate the incidence of heparin induced thrombocytopenia and to identify its types and the severity of each type and also to discuss and compare the effect of different risk factors on each type.

KEYWORDS: HIT; Al-salam general hospital; Heparin Leo; patients

INTRODUCTION

Heparin induced thrombocytopenia (HIT) is one of the important and common side effect of heparin therapy.

DEFINITION OF HIT

The normal range of platelet count is 150- 450 * 10^9/L [5]. HIT is defined as a reduction of platelet count > 50% of the baseline or reduction to less than 150 * 10^9/L with reduction not less than 30% of baseline [6]. HIT must be distinguished from other forms of drug induced thrombocytopenia because of its potentially catastrophic thrombotic complications and its unique pathophysiology [3].

HEPARIN

Standard unfractionated heparin is a highly sulphated glycosaminoglycan [4], that is partially purified from either porcine intestinal mucosa or bovine lung [7], its molecular weight ranges from 3000-30000 Dalton with average of 15000 Dalton [2]. Heparin acts primarily by binding to antithrombin III (AT III) an enzyme that inhibits the coagulation factors thrombin (factor IIa), Xa and IXa [4]. Heparin subsequently promotes a

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conformational change in AT III that accelerates its activity approximately 100-1000 folds [4]; this prevents additional thrombus formation and permits endogenous fibrinolytic mechanisms to lyse clot that has already formed. However, heparin dose not directly dissolve thrombus that already exists [4].The efficacy of heparin is limited because clot bond thrombus is protected from heparin–antithrombin III inhibition. Furthermore, heparin resistance can occur because unfractionated heparin binds to plasma proteins (including acute phase reactants) and to vascular endothelial and blood cells [4]. Heparin is poorly absorbed from the gastrointestinal tract and therefore must be administered parenterally [2].

Two types of thrombocytopenia are associated with heparin therapy.

HEPARIN INDUCED THROMBOCYTOPENIA TYPE ONE (HIT1)

This type of HIT usually occurs during the first 4 days of heparin therapy and usually occurs in-patients receiving therapeutic doses of heparin [7].

HEPARIN INDUCED THROMBOCYTOPENIA TYPE TWO (HIT2)

This type of HIT is usually immunological in origin and it occurs characteristically 5-8 days after starting heparin therapy [8].

HIT1: This type is a common form of HIT; the reported incidence may reach up to 30% and it has a benign and self-limited side effects. This dose dependent type of thrombocytopenia usually occurs with large doses of heparin and it rarely causes severe reduction in platelet count (platelet count not less than $60*10^9$/L) [2][4], and it rarely causes clinical complications and usually dose not require discontinuation of heparin therapy and is probably caused by the direct agglutinating effect of heparin on platelet. The higher molecular weight of heparin binds with higher affinity to platelet probably because of their increase total negative charge [9]. Test for heparin dependent antiplatelet antibodies is negative in this type.

HIT2: This type is usually less common form of HIT [10]. It is this type of thrombocytopenia which makes the whole clinical significance of HIT. The incidence is about 1-5% [11], it is immunological in origin and it paradoxically causes serious and life threatening arterial as well as venous thrombosis [12]. The decline in platelet count is usually moderate to severe with typical nadir of 50-60 * 10^9/L [4]. However, the reduction in platelet count can be more severe with or without thrombosis and conversely heparin induced thrombocytopenia (positive antibody testing) can actually occur with a normal platelet count.

The mechanism of this type of HIT is the interaction of antibody (usually IgG) with a complex of heparin and heparin binding cataionic protein (platelet factor four (PF4)) [13], which is secreted from platelet alpha-granules and then binds to platelet and endothelial cell surface [14, 15]. Antibodies may bind to heparin complexed with PF4 on platelets or endothelial cells or bind to heparin-PF4 complex in plasma [16] with the resulting trimolecular complex which then binds to platelet surface FCγIIa receptor (FCγRIIa) [17].

These immune complexes have the ability to activate platelets and generate procoagulant membrane microparticles which may contribute to the thrombotic complications of HIT [18]. Although, HIT2 usually develops with therapeutic doses of I.V. or S.C. heparin it can develop with low dose heparin or heparin flushes or the use of heparin bound catheters [12]. Thrombosis with potentially severe and fatal complications is the most serious adverse reaction to heparin [5, 19, 20], but the frequency of this complication is unknown, different studies show different incidence ranging from 25-50% of cases of HIT2 [5].

Venous thrombosis is more common than arterial thrombosis [12]. Deep vein thrombosis and pulmonary embolism were the most common events [15]. Arterial thrombotic events mainly include; limb ischemia, myocardial infarction and stroke [4]. Figure [5] show the skin thrombotic complication of HIT [18].

Most thrombotic events usually occur in the first week after diagnosis of HIT and those who develop thrombosis usually have a high mortality and morbidity. In a review of 32 such patients 5 died (15.6%) and 3 (9.37%) required limb amputation [4].

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Warfarin treatment after stopping heparin has been reported to cause venous limb gangrene presumably as a result of protein C depletion [21]. However, these complications may have been related to excessive warfarin doses that caused rapid decline in protein C before producing anti coagulation by reducing the plasma level of the long lived procoagulant prothrombin and factor X [22].

HIT and thrombosis is best avoided by beginning warfarin and heparin simultaneously at the initiation of anticoagulation treatment. This allows therapeutic warfarin anticoagulation to become established in about 5 days which is before heparin induced thrombocytopenia is likely to occur [22].

Other rare allergic reactions have been reported which occurred simultaneously with the onset of HIT such as severe anaphylaxis with cardiopulmonary arrest [23].

LAB DIAGNOSIS OF HIT

Two general types of lab assays have been described (8,24).

1. Functional assays:

Which are based on platelet aggregation and secretion.

2. Antigen assays:

Which are based on ELISA using heparin-PF4 as the target antigen.

The principle of the functional assays includes the incubation of patient's serum and heparin with normal platelet and the aggregation or secretion responses of platelet is measured [25]. However, the execution of the assays may be difficult since platelet responsiveness varies among different normal donors, with platelet from some normal donors being completely unresponsive [26], and apparent spontaneous platelet aggregation or secretion in these assays may be caused by the presence of trace amount of residual thrombin in the sera [5].

The most widely described tests are functional assays using as end points aggregation or the secretion of C14 - serotonin from normal platelets preincubated with C14 – serotonin [8].

Although these assays can support a clinical diagnosis of HIT they may also be positive in patients with no thrombocytopenia, even patients with no history of heparin exposure, these assays have not been adapted to routine clinical

laboratories [27].

ELISA assays are easily adaptable to routine clinical laboratories but their clinical values are uncertain. Direct comparison of the ELLSA assay with functional assay C14 – serotonin secretion or aggregation demonstrate general agreement and in each study the ELISA identified more patients as positive suggesting greater sensitivity [29], however, again multiple studies have reported these antibodies in patients with no thrombocytopenia, even patients with no history of heparin exposure [4].

Thus at present the positive and negative predictive value of these tests remain unknown. When HIT is suspected heparin must be stopped [27]. No lab test has been validated by demonstrating the safety of continuing heparin when a negative results is reported [2], similarly a positive ELISA assay dose not necessarily confer a high risk of having thrombocytopenia.

MATERIALS & METHODS

Two hundred patients 120 males and 80 females (all in alsalam General Hospital) who received intermittent standard heparin therapy for different medical indications were included in the study. The sample was collected in 7 months period from the first day of February to the end of August 2022.

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THERAPY

All patients received heparin sodium of porcin gut origin (heparin Leo) by intermittent I.V. route in a dose of 5000-7500 units six hourly. The duration of therapy ranged from 4-10 days (mean 7 \pm 2.7).

INCLUSION CRITERIA

Any patient with medical condition who received heparin therapy more than 3days.

EXCLUSION CRITERIA

- Any patient whose baseline platelet count less than 150×10^9/L.
- Any patient with medical condition known to induce thrombocytopenia like ITP, sepsis and DIC etc.
- Patient receiving drugs known to affect the platelet count like quinidine, Rifampicin, Methyl dopa etc.[2].

The information which are collected from the cases under study were taken according to the following questioner:

QUESTIONER

*Serial No. :

*Name : *Age :

*Sex : *Residence :

*Occupation:

*Date of admission:

*Date of discharge:

*Short history and clinical presentation :

*Previous history of :-

IHD : Smoking :

D.M : H.T :

*Previous heparin exposure:

*Time and duration of previous exposure:

*Indication for heparin administration :-Acute coronary syndrome:

Ischemic Stroke : Deep vein thrombosis : Others :

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*Level of platelet count:-

Base line : [ ] Day 2 : [ ]

Day 4 : [ ] Day 7 : [ ]

Day 11 : [ ] Day 14 : [ ]

Other days: [ ]

*Complications:

*Notes:

*Patient medications before admission:

*Medications received during admission:

*Duration of heparin therapy:

*Dose of heparin therapy:

LABORATORY TESTS

Complete blood count including platelet count were performed before heparin administration or within the first 24 hour of initiation of heparin therapy, the platelet count was also performed in days 2, 4, 7, 11 and 14 respectively, and in those who developed significant reduction in platelet count more frequent checking of platelet count were performed. 2.5 ml of venous blood was taken in an EDTA tube, platelet count was determined by improved Neubauer counting chamber or known as squares method; a slide with squares in the center, counting the platelet in 25 chambers or squares and their total number multiplied by 10^9 is the platelet count per liter [28]. The same physician did all platelet count and when thrombocytopenia is detected another sample was taken right away to verify the thrombocytopenia. Heparin therapy was adjusted to keep the activated partial thromboplastin time between 2-3 times that of control.

RESULTS

Our study was done to evaluate the incidence of HIT and included 200 patients with different medical indications for heparin administration.

Table No. (1) shows the general characteristics of the sample taken in regard to sex, age, indication for heparin therapy, history of previous exposure to heparin and percent of affected cases. The total number was 200 patients. Aged from (17-81) years with median age of about 53 years. The affected cases with heparin induced thrombocytopenia were 16 (8%) cases, 10(5%) males and 6 (3%) females. The patients who for the first time exposed to heparin were 162 (81%) cases and those with second time or more exposure where 38 (19%) cases.

Regarding the indication for heparin therapy, 124 (62%) were due to acute coronary syndrome (Myocardial infarction, unstable angina), 54 (27%) cases due to cerebrovascular ischemic strokes, 20 (10%) cases are due to DVT and two (1%) other cases one due to cavernous sinus thrombosis and the other case was arterial thromboembolism of the left arm.

Table No. (2) shows the percentage of affected patients in relation to their age, the patients were classified into four main age groups as follows: < 40, 40-50, 51-65 and > 65 years old and the number of affected patients in each age group was as follows 1, 5, 8, 2 cases respectively. No age group has statistical difference from other groups. Fig. (1) shows the percentage of affected cases in each age group.

The effect of the various medical indications for heparin administration on the incidence of HIT in its both types is evaluated, Table No. (3) and Fig(2) shows the number of affected cases for each medical indication.

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Table No. (4) describe the level of platelet count in the affected cases and the time of onset of HIT. Of the (16) affected cases, (8) cases developed reduction in platelet count in the first 2 days and another (4) cases added at day 4, while another (3) cases developed the reduction at day 7 and the last one was discovered at day 11. Figure (3) summarizes these results.

The severity of thrombocytopenia in the two types of HIT is compared and this is shown in table (5), the percent reduction in platelet count is divided into moderate reduction in which platelet count is reduced from 30-50% of baseline and severe reduction in which platelet count reduced > 50% of baseline.

Table (5) show that (3) cases of HIT2 out of (4) cases were severely reduced and only (2) cases of HIT1 out of (12) cases have severe reduction in platelet count.

The influence of previous heparin exposure on the incidence of HIT is studied, and of (162) cases who first exposed to heparin, 13 cases were affected, while of (38) cases who have previous heparin exposure, 3 cases were affected. As shown in Table (6).

And in order to evaluate the influence of previous heparin exposure on the severity of HIT, patient with first exposure to heparin and those with previous exposure is compared in each type of HIT as shown in Table (7).

DISCUSSION

In our study we evaluated the incidence of HIT in patients receiving intermittent I.V. heparin therapy and we tried to assess the general characteristics of the 2 types of HIT.

The general characteristics of the patients under study were shown in Table (1). Of 200 cases, 120 (60%) patients were males and 80 (40%) patients were females with male: female ratio of 3:2. The percentage of affected cases is not statistically significant in respect to their sex. The number of affected cases in our study was 16 (8%) cases.

The reported incidence of HIT in several other studies is ranged from 1-32% (4).

The difference in incidence in different studies could be due to the following reasons:

Definition of thrombocytopenia: different cut of levels of platelet count are used to define HIT, some studies used 150×10^9/L, others used 100×10^9/L (5,12).

Different types of heparin (bovine versus porcine) used and each type came from different lot (31). In our study we used one lot of porcine heparin.

The duration of heparin therapy and frequency of platelet count determination was not uniform among different studies (12), it ranged from 3 to 10 days, so if a patient is monitored for only few days, the delayed type of HIT might not be

detected.

Other variable factors include the rout of heparin administration (continuous or intermittent intravenous infusion or subcutaneous), the dose of heparin used and the diluent and tubing used to administer heparin.

The affected cases were classified according to their age into four groups as shown in table (2) and Fig. (1) and in all these age groups the incidence of HIT was statistically not significant (X^2 test is used as a test of significance (32)).

Another classification of the cases under study was according to the medical indication for heparin administration, the 3 major indications were related to the cardiovascular system, acute coronary syndrome (myocardial infarction, unstable angina), cerebrovascular system (ischemic stroke) and deep vein thrombosis. The frequency of affected cases for each indication is shown in Table (3), no one was superior

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to other in increasing the frequency of HIT (i.e., no statistically significant results between different indications).

We classified HIT into 2 types: -

Type One: Is thrombocytopenia which occurred in the first 4 days of heparin therapy, is a common complication, 12 cases (6%) were reported and it was a moderate form of thrombocytopenia, lasting 2-5 days (mean 3 ± 1.5) and platelet count returned to normal levels even when heparin therapy is maintained, no complications have been reported with this type of thrombocytopenia, most of the cases (10 out of 12 cases) were taking heparin for the first time.

Type Two: Is thrombocytopenia which starts more than 4 days after the onset of heparin therapy, this type of thrombocytopenia is usually associated with severe reduction in platelet count to less than 40-50% or more, its usually less common than HIT1 (4 reported cases (2%)) and usually immunological in origin due to the development of IgG to platelet factor 4-heparin complex. It's this type of HIT which makes the whole clinical significance of heparin induced thrombocytopenia because it usually associated with severe form of venous and arterial thrombosis. The characteristics of the 4 affected patients with HIT2 are shown in Table (8). This type of HIT usually starts in day 5-8 and it usually becomes more severe if heparin therapy is continued, it reached in one case to 26% of the baseline platelet count.

In all 4 affected cases heparin was stopped upon diagnosis of HIT and platelet count start to rise again and reached its near normal level in about 5-10 days (mean 8 ± 2.5). Figure (4) show a classical case of HIT in its both types in relation to both severity of thrombocytopenia and time of onset of HIT.

The severity of thrombocytopenia in each type of HIT is assessed.

HIT2 was more severe than HIT1, the difference was statistically significant at (P value 0.05) as shown in table (5) and this could be due to the difference in the mechanisms of induction of thrombocytopenia.

Table (6) show the incidence of HIT in respect to the history of previous heparin exposure, there were no statistically significant difference between the first time exposure or previous exposure to heparin, i.e. the incidence of HIT is not affected by previous heparin exposure.

The severity of thrombocytopenia of the affected cases that received heparin for the first time to those who have previous history of heparin exposure is also compared; the study showed the following:

In patients with HIT2, there were no statistical difference in the severity of the 2 groups (P value was not significant) while; in patients with HIT1, the severity was high in patients who received heparin for the second time (2 cases) in comparison to those who received heparin for the first time (both the 2 cases have received heparin in the last 6 months) and this can be explained by the presence of antibodies to heparin which developed due to the first exposure (the same pathophysiology of HIT2) and this go with one study done by Warkentin TE and Kelton JG which showed that 30% of patients who were known cases of HIT developed severe form of thrombocytopenia on readministration of heparin in the first 4 days, and in all these cases IgG to heparin were positive). In those two cases one of them received heparin for 3 days then when thrombocytopenia discovered heparin stopped and platelet count rose again and reached normal level five days later on, while the other one was discharged from hospital on his responsibility. Table (7) show these figures.

In about 50 cases (25% of total cases) platelet count was mildly reduced (10-24% of baseline) and in all these cases the reduction in platelet count was in the first few days of heparin therapy, and in most of them heparin was maintained and the platelet count regain to baseline level with no obvious complications.

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Table 1. Characteristics of Patients who are exposed to heparin therapy.

Character	Affected cases (No.)	Affected cases (%)	Not affected cases (No.)	Not affected cases (%)	Total (No.)	Total (%)
No.:	16	(8)	184	(92)	200	(100)
Sex:						
Males	10	(5)	110	(55)	120	(60)
Females	6	(3)	74	(37)	80	(40)
Age (year):						
Males	52.28 ±11.2*		53.08 ± 11.9*		52.67 ± 11.5*	
Females	53.75 ±13.8*		54.26 ± 11.6*		53.96 ± 12.7*	
Heparin Administration:						
1st time exposure	13	(6.5)	149	(74.5)	162	(81)
Previous exposure	3	(1.5)	35	(17.5)	38	(19)
Indication for administration:						
ACS	10	(5)	114	(57)	124	(62)
CVA	4	(2)	50	(25)	54	(27)
DVT	2	(1)	18	(9)	20	(10)
Others	0	(0)	2	(1)	2	(1)

± values are 1 standard deviation (SD) from the mean.

Table 2. Distribution of affected cases with HIT according to different age groups.

Age group (yr)	Affected cases No.	Affected cases (%)	Not affected No.	Not affected (%)	Total No.	Total (%)	Significance
< 40	1	(0.5)	19	(9.5)	20	(10)	N.S.
40-50	5	(2.5)	64	(32)	69	(34.5)	N.S.
51-65	8	(4)	74	(37)	82	(41)	N.S.
> 65	2	(1)	27	(13.5)	29	(14.5)	N.S.
Total	16	(8)	184	(92)	200	(100)	

N.S. : Not significant.

Table 3. Distribution of affected cases according to different medical indications for heparin administration

Indication	Affected cases HIT1	Affected cases HIT2	Not affected	Total
ACS (MI, US)	7	3	114	124
CVA	3	1	50	54
DVT	2	0	18	20
Others	0	0	2	2
Total	12	4	184	200
Indication	X^2	O.R.	P. value	Significance
ACS	0.2	1.09	> 0.05	N.S.
CVA	1.3	0.72	> 0.05	N.S.
DVT	0.7	1.02	> 0.05	N.S.

ACS : Acute coronary syndrome. CVA : Cerebrovascular accident. DVT : Deep vein thrombosis

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Table 4. Levels of platelet count in the affected cases.*

No.	1st platelet	Day 2 (%)	Day 4 (%)	Day 7 (%)	Day 11 (%)	Day 14 (%)
1	220	198 (10)	154 (30)	116 (48)	143 (35)	176 (20)
2	260	129 (51)	169 (35)	208 (20)	248 (5)	X
3	223	200 (10)	135 (46)	190 (15)	210 (5)	X
4	255	148 (42)	190 (25)	240 (6)	270 (-6)	248 (3)
5	225	146 (35)	180 (20)	207 (8)	X	X
6	350	319 (9)	234 (33)	171 (51)	210 (40)	260 (26)
7	239	144 (40)	155 (35)	191 (20)	212 (12)	224 (6)
8	210	143 (32)	189 (10)	214 (-2)	200 (4)	X
9	220	150 (25)	143 (35)	173 (21)	187 (15)	205 (7)
10	230	147 (36)	196 (15)	207 (10)	216 (6)	220 (4)
11	300	150 (50)	165 (45)	200 (34)	204 (32)	240 (20)
12	240	190 (21)	136 (43)	199 (17)	216 (10)	X
13	280	258 (8)	224 (20)	140 (50)	66 (74)	182 (35)
14	220	145 (34)	174 (21)	200 (9)	X	X
15	210	164 (22)	132 (37)	181 (14)	190 (10)	206 (2)
16	305	314 (-3)	275 (10)	167 (45)	137 (55)	177 (42)

** Dashed lines indicate the time of onset of HIT.*

Table 5. The Severity of thrombocytopenia in both types of HIT.

Type of HIT	Moderate	Severe	Total
HIT_1	10	2	12
HIT_2	1	3	4
Total	11	5	16

X^2 = 4.74 which is significant at P value 0.05.
O.R. = 0.067 and C.I = (0.005 - 0.76).

Table 6. The distribution of affected cases of HIT according to the history of previous heparin exposure.

Type of HIT	Affected cases	Not affected cases	Total
1st heparin exposure	13	149	162
Previous heparin exposure	3	35	38
Total	16	184	200

X^2 = 0.2 which is not significant.

Table 7. The severity of thrombocytopenia in both types of HIT in relation to heparin administration.

HIT1

Heparin administration	Percent reduction in platelet count
1st exposure	51, 42, 35, 40, 32, 35, 36, 43, 34, 37
Previous exposure	46, 50

F test = 4.96 which is statistically significant At P value = 0.05.

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HIT2

Heparin administration	Percent reduction in platelet count
1st exposure	48, 51, 74
Previous exposure	55

F test = 0.8 which is not significant.

Table 8. Characteristic features of patients with HIT2.

No.	Sex	Age	Diagnosis	Baseline platelet count (10^3 m^3)	Onset of thrombocyteopenia (days)	Lowest platelet count ($10^3/m^3$)	Day of lowest count	% drop in plat eletcount	Days of recovery	Ischemic event	Outcome
1	M	56	MI	220	4	116	7	48	7	Nil	Improved
2	F	48	UA	350	7	171	7	51	5	Nil	Improved
3	M	60	CVA	280	6	66	11	74	9	Nil	Improved
4	M	45	MI	305	7	137	9	55	6	Nil	Improved

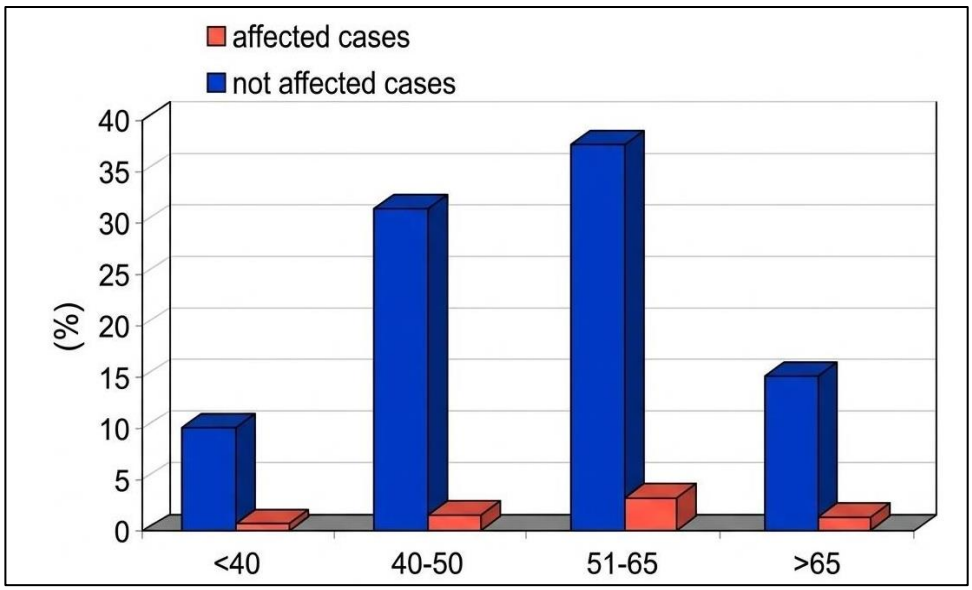


Fig. 1. Percentage of affected cases with HIT for each age group

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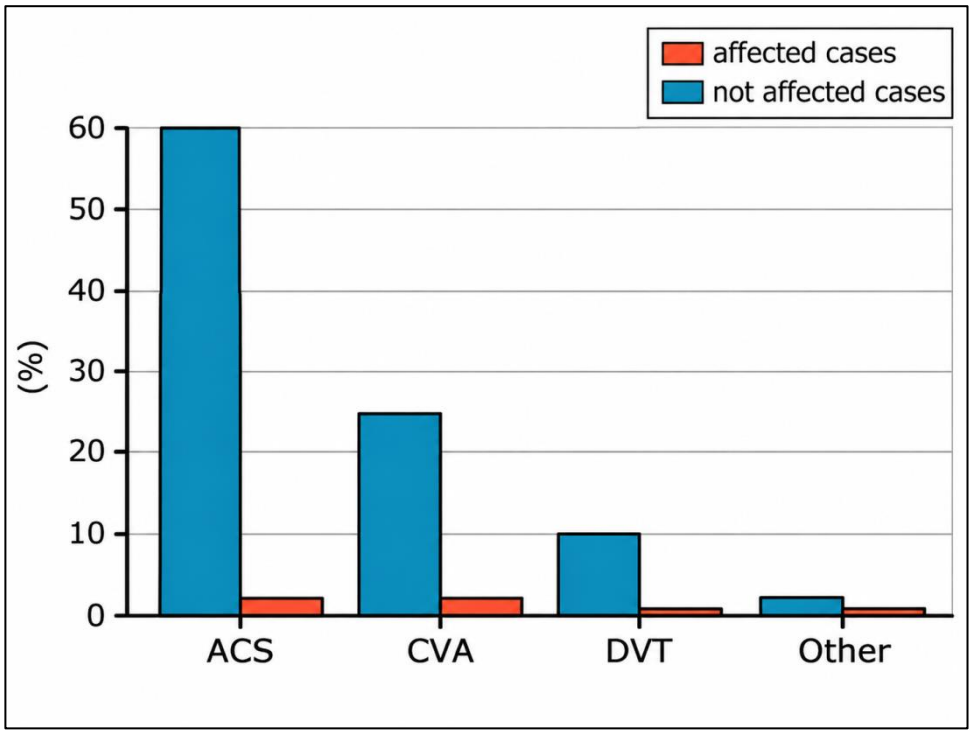


Fig. 2. Precentage of affected cases with HIT different medical indications for heparin administration

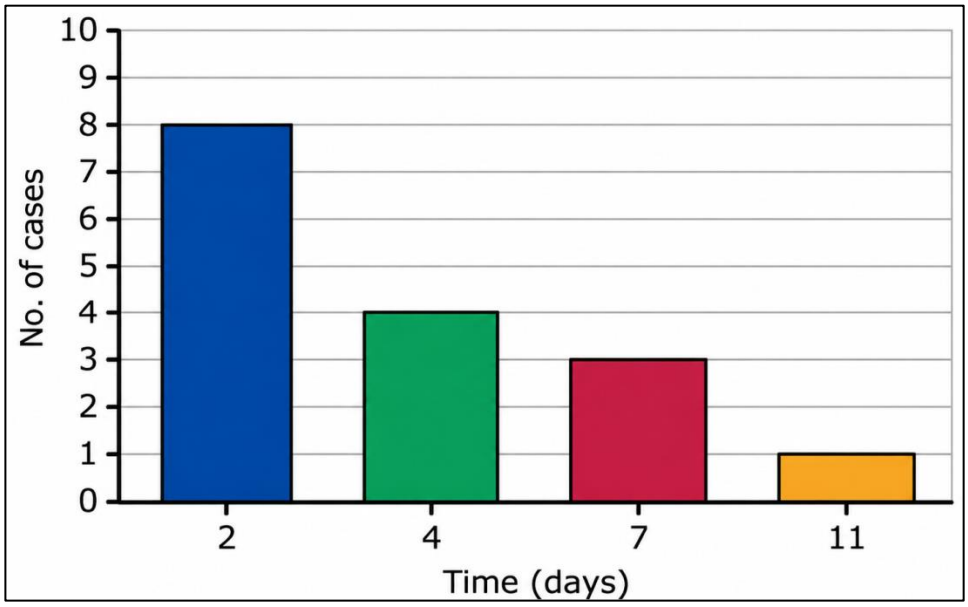


Fig. 3. Time of onset of Hit in affected cases

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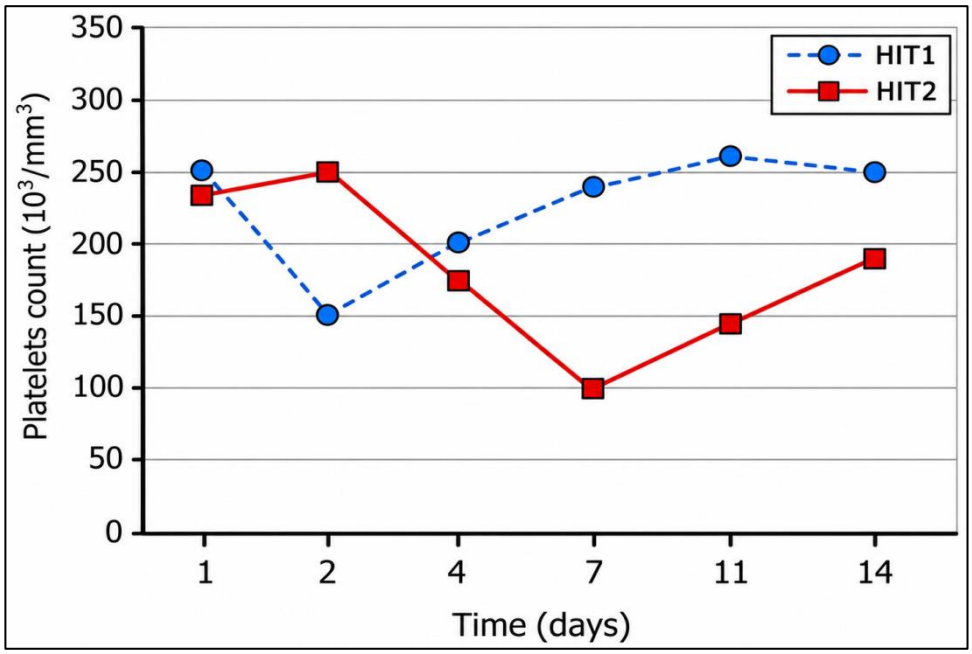


Fig. 4. Representative case showing the drop in platelet counts in HIT1 & HIT2



Fig. 5. The skin complication of HIT

CONCLUSIONS AND RECOMMENDATIONS

Heparin induced thrombocytopenia is a common complication of heparin therapy 2 types of HIT is described, the first one usually occurs in the first few days of heparin therapy and is common, mild-moderate type and need not to stop heparin therapy, and other late onset type is immunological in origin, severe in type and may be associated with thrombotic complications and when this type of HIT is discovered, heparin must be stopped. The incidence of this type is (2%), no thrombotic complications have been reported and the platelet count returned to normal level after cessation of heparin therapy.

We recommend that clinicians treating patients with heparin should be aware of HIT and they should

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determine platelet count at baseline and hence forth at regular intervals beginning from the fourth-fifth days of therapy and earlier in patients with previous history of heparin exposure.

We also recommend to use the shorter course of heparin therapy and to commence warfarin therapy with the start of heparin and to discontinue heparin 3-5 days once warfarin effect has started and the targeted prothrombin time is achieved.

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