WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 16, 746-756. Research Article ISSN 2277– 7105

# INCIDENCE OF HEPARIN INDUCED THROMBOCYTOPENIA INA TERTIARY HOSPITAL

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Article Received on
21 June 2018,

Revised on 11 July 2018,
Accepted on 01 August 2018

DOI: 10.20959/wjpr201816-13096

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## ABSTRACT

**Objective:** The incidence of heparin induced thrombocytopenia(HIT) after treatment with unfractionated heparin and low molecular weight heparin when used prophylactically or therapeutically is largely unknown from India. **Methodology:** A Prospective descriptive study, consisting of hundred patients fulfilling the inclusion criteria, was undertaken at Bangalore Baptist Hospital, Bengaluru, between August 2009 to July 2011. Patients were treated with heparin prophylactically or thereupeutically. The type of heparin used that is low molecular weight heparin(LMWH) or unfractionated heparin was on treating physician's discretion. The platelet count was monitored on day of admission and day five and the day just before discharge. The complications like major/minor bleeding were continuously monitored. **Results:** In this study that there was 4% incidence of thrombocytopenia in unfractionated heparin group. Incidence of HIT in LMWH was none. The patients who developed bleeding manifestations were less than 1% and none of them required any interventions among patients who developed thrombocytopenia. **Conclusion:** Unfractionated heparin can be safely used which is more cost effective, especially in prophylactic use, provided people are on the lookout for this complication for thrombocytopenia and bleeding manifestations, particularly with therapeutic use.

**KEYWORDS:** HIT in LMWH.

## INTRODUCTION

Heparin induced thrombocytopenia first reported in 1973, remains largely under-diagnosed and unrecognized. Routine platelet count measurements were not routinely performed until the 1970s. This may explain why thrombocytopenia was not reported in the first 24 patients

with heparin-induced arterial emboli.[1,2]

In 1969, the term "Heparin-Induced Thrombocytopenia" was used by Natelson[3] to describe a 78-year-old man with pulmonary embolism who developed severe thrombocytopenia after heparin.

There are two types of heparin induced thrombocytopenia Heparin induced thrombocytopenia Type 1 is more common with an incidence of 10-20%[4,5,6] but with no significant clinical consequences. It is less life threatening with a much lower incidence of complications like bleeding or thrombosis. It occurs within the first two days after heparin therapy. It is self limiting and treatment consists of stopping heparin along with supportive measures. Thrombocytopenia clears up within days.

Heparin induced thrombocytopenia type II is a less common, antibody mediated thrombocytopenia but has serious complications like thrombosis that can lead to devastating thromboembolic complications, including pulmonary embolism, ischemic limb necrosis necessitating limb amputation, acute myocardial infarction, stroke involving other organs and has a high reported mortality rate. The first to identify the central features of the HIT syndrome—thrombocytopenia, thrombosis, and its immune pathogenesis—were Drs. Silver, Rhodes, and Dixon.[7]

In their 1973 paper, they described 2 patients with severe thrombocytopenia, myocardial infarction, and heparin resistance, with platelet count recovery on discontinuing heparin treatment. Both patients developed rapid recurrence of thrombocytopenia when heparin rechallenges were given.

An immune basis for this syndrome was suggested by increased numbers of bone marrow megakaryocytes and a rapid recurrence of the thrombocytopenia upon heparin re- exposure.

A circulating heparin-dependent, platelet-activating substance (subsequently identified as IgG) was found in the patients' blood, which caused aggregation of donor platelets in the presence of heparin.

A subsequent report by Rhodes and coinvestigators8 helped establish HIT as a distinct syndrome.

Eight patients were described with thrombocytopenia (platelet count nadir, 25 x109/L) that occurred during heparin administration.

Thrombotic, rather than hemorrhagic, complications predominated 7 patients had new or recurrent thromboembolic events, and one patient had a hemorrhagic stroke.

Complement-fixing, heparin-dependent antibodies were found in blood from 5 patients. It is rare for a prothrombotic disorder to cause both arterial and venous thrombosis. HIT is an exception. In many HIT patients there was evidence of hypercoagulability, but the pathway that could initiate both arterial as well as venous thrombosis remained unexplained.

Three explanations were proposed:

1. HIT antibodies could bind to and injure endothelial cells, thereby initiating coagulation.[9,10]
2. HIT antibodies could bind to monocytes and release tissue factor.[11,12]
3. HIT antibodies induce a platelet procoagulant response.

There are very few studies among Indian population regarding the effects of heparin on platelet count, its complications and the cost effectiveness. This instigated the pursuance of this study.

## MATERIALS AND METHODS

1. Men and non-pregnant women above the age of 18yrs were included in the study.
2. Detailed clinical history and examination.
3. Baseline platelets were obtained within 24hrs of admission and repeated after 5 days or before discharge whichever was later.
4. Diagnosis of HIT was based on:

- More than 50% decrease in platelet count after exposure to heparin.
- Timing of the decrease in platelet count compatible with HIT.
- A new thrombosis, skin necrosis or an acute systemic reaction after heparin administration.
- Absence of other causes of thrombocytopenia.

The type of heparin used was on the choice of the treating physician The primary objectives of the study were to find the Incidence of HIT. Difference between low molecular weight

heparin and unfractionated heparin in heparin induced thrombocytopenia with special reference to cost effectiveness. The secondary objectives were to find the Temporal pattern of thrombocytopenia in relation to initial use or re-exposure to heparin, The time interval between the heparin exposure that resulted in HIT and the previous heparin exposure if any and if there was any association between the route of heparin administration [intravenous (i.v) or subcutaneous (sc)]. Any bleeding complications were also monitored.

**Inclusion Criteria**

Men and non pregnant women aged more than 18yrs admitted to hospital and who are put on therapeutic/prophylactic doses of heparin.

**Exclusion Criteria**

- Sepsis and cancer-associated DIC as defined by history (e.g., sepsis, trauma, malignancy), clinical presentation, moderate to severe thrombocytopenia (<1lakh/microL) and the presence of microangiopathic changes on the peripheral blood smear.
- DIC (multiple causes besides HIT).
- Drug induced thrombocytopenia (other than heparin) -- Abciximab, Quinine and quinidine, Sulfonamides, Vancomycin, Gold compounds, Beta-lactam antibiotics, Valproic acid, Measles- mumps-rubella vaccine.
- Thrombolytic therapy.
- Thrombotic thrombocytopenic purpura.
- Patients with documented bleeding or thrombophilic disorder.
- Patients undergoing surgery
- Any contraindication to heparin.

**Statistical analysis**

**Statistical Methods:** Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean  SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The following assumptions on data is made.

**Assumptions**

1. Dependent variables should be normally distributed,

2. Samples drawn from the population should be random. Cases of the samples should be independent

**Statistical software:** The statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.

**Study Design**: A comparative two groups 100 patients, 50 patients with low molecular weight and 50 patients in unfractionated heparin is undertaken to:

- Study the Incidence of thrombocytopenia in unfractionated heparin and low molecular weight heparin.
- Factors like age/sex/premorbidities like hypertension, diabetes, IHD, CKD hold any significance in thrombocytopenia.
- If there any effect on platelet counts on re-exposure of heparin.
- Cost effectiveness between low molecular weight heparin and unfractionated heparin.
- Any bleeding complications

## OBSERVATION AND RESULTS

**Table 1: Baseline characteristics of patients studied in two groups.**

| | Low molecular weight heparin (n=50) | Unfractionated heparin (n=50) | p value |
|---|---|---|---|
| Age in years | 54.46±15.19 | 50.40±16.37 | 0.202 |
| Male | 31(62.0%) | 26(52.0%) | 0.419 |
| Female | 19(38.0%) | 24(48.0%) | |
| Hypertension | 21(42.0%) | 20(40.0%) | 0.839 |
| DM | 12(24.0%) | 1(2.0%) | 0.001** |
| IHD | 4(8.0%) | 1(2.0%) | 0.169 |
| CKD | 3(6.0%) | 2(4.0%) | 0.646 |
| Admission platelet count | 222660.00±45201.86 | 266080.00±51321.25 | <0.001** |

The aim of this study was to find out the incidence of thrombocytopenia in patients treated with heparin in our setting.

Type I and Type II heparin induced thrombocytopenia could not be differentiated in this study as it requires serology tests like serotonin assay and heparin PF4 ELISA. Two study groups were taken who fulfilled the inclusion criteria, 50 patients in unfractionated heparin group and 50 patients in low molecular weight heparin group.

The present study showed that there was 4% incidence of thrombocytopenia in unfractionated heparin group and they, did not require any intervention. The incidence of heparin induced thrombocytopenia in low molecular weight heparin was 0%. The maximum reduction of

platelet count seen in low molecular weight heparin was 13.74% when compared to 50% reduction to qualify for HIT.

Thrombotic complications were nil in our group of patients who received heparin in either form. Both arterial and venous thromboses were taken into consideration. Clinical manifestations like deep vein thrombosis, cerebrovascular accidents of both artery and vein, gangrene were closely monitored.

Duration of heparin therapy is not associated with thrombocytopenia or bleeding manifestations within ten days of therapy in this study. This was taken into consideration as some studies showed the longer duration of heparin therapy was associated with higher incidence of th,rombocytopenia.

There were 5 patients who received bolus intray. enous unfractionated heparin and they did not have a higher incidence of thrombocytopenia. Only one patient among them had minor bleeding thus suggesting route of administration is not significant both statistically and clinically.

Also the dose of heparin used is not related to thrombocytopenia or bleeding complications. Patients receiving heparin either prophylactically or therapeutically did not have any difference in the incidence of thrombocytopenia. HIT is mainly an antigen antibody mediated reaction and is not related to the dose used.

Also patients aged more than 40 years had a higher incidence of thrombocytopenia with incidence of 4%. The exact reason for this higher incidence of thrombocytopenia with higher age is unknown. Similar finding is noted in other studies.

It was seen in this study that re-exposure to heparin in patients receiving heparin (either low molecular weight heparin or unfractionated heparin) did not carry a higher risk. 24% of the patients in low molecular weight heparin group and 16% in the unfractionated heparin group had re-exposure to heparin and they did not have a higher incidence of thrombocytopenia. The maximum reduction in the platelet count seen in unfractionated heparin group was 35.13% drop and in low molecular weight heparin was 9.09%.

In this study males were found to have higher incidence of thrombocytopenia compared to females. The exact cause for this could not be found out. Some Studies done earlier higher

incidence among females. However the relation between gender and HIT is under research.

This study had 5 chronic kidney disease patients on dialysis and none of them developed heparin induced thrombocytopenia. All of them were receiving 5000 units of unfractionated heparin regularly during their dialysis.

Also noted during this study was patients who developed maximum reduction in platelet count though not qualifying for HIT were CKD patients on dialysis. Thus indicating some relation between thrombocytopenia and heparin. The maximum reduction in platelet count was 9.09% in LMWH and 35.13% in unfractionated heparin group respectively.

Total cost of treatment for unfractionated heparin was significantly lower when compared to the low molecular weight heparin group. Per day cost for low molecular weight heparin is approximately Rs.500 and for unfractionated heparin Rs.100.

As the difference between the two types of heparin is marginal with respect to incidence of thrombocytopenia and bleeding complications, it may be suggested that in our ICU'S unfractionated heparin may be used at least for prophylactic purposes as it is more cost effective. A repeat platelet count on $5^{th}$ day and the day before discharge and clinical observation is enough to pick up heparin induced thrombocytopenia.

**DISCUSSION**

Studies done in the past shows a varied incidence in HIT. The incidence of HIT in unfractionated heparin group varies from as low as 1-5% 13 to 36.4%[14] and low molecular weight heparin from 015 to 2.2%.[16] There are not many Indian studies on the incidence of thrombocytopenia with the use of heparin. Hence more studies on larger population id necessary to know the incidence of HIT and its complications.

In this study done there was only 4% incidence of thrombocytopenia among the unfractionated heparin group with none of them requiring any intervention and none in the low molecular weight heparin developed thrombocytopenia.

HIT is a pro thrombotic state with a reported incidence of 19-52% thromboembolic events.[17] However in this study the two patients who developed thrombocytopenia did not develop any thromboembolic events.

Also the previous studies showed an incidence of 15%-20% 18-19 of thrombocytopenia on prolonged exposure to heparin. However in this study it was concluded that duration of heparin therapy and HIT is unrelated.

Re-exposure to heparin was taken into consideration and the two main groups of patients were clubbed together. That is the patients who had received heparin either prophylactically or therapeutically for any reason during the previous admission and chronic kidney disease patients who receive heparin during dialysis. It was noted that there was no significant drop in the platelet count with the re-exposure or CKD patients. 9.09% drop in platelet count in low molecular weight heparin group and 35.13% in unfractionated heparin group was seen. This is in comparison with the studies done earlier in which the risk of HIT after LMWH is increased in those with prior exposure to heparin therapy.[20] This was reported in a prospective cohort study in 1754 consecutive medical patients treated with LMWH in which the overall incidence of HIT was 0.8 percent.

A Similar study showed that there was higher morbidity and mortality in patients with chronic kidney disease due to heparin induced thrombocytopenia.

**Table 2: Incidence of thrombocytopenia in two groups studied.**

| Thrombocytopenia | Low molecular weight heparin | | Unfractionated heparin |
|---|---|---|---|
| | No. | % | No. |
| No | 50 | 100.0 | 48 |
| Yes | 0 | 0.0 | 2 |
| Total | 50 | 100.0 | 50 |
| Inference | Incidence of thrombocytopenia is 4% in unfractionated heparin with no thrombocytopenia in low molecular weight heparin | | |

**Table 3: Distribution of bleeding manifestations in unfractionated heparin group.**

| Bleeding manifestations | Number of patients (n=2) | % |
|---|---|---|
| Haematuria | 1 | 50.0 |
| Petechiae | 1 | 50.0 |
| Inference | There was mild bleeding seen in the unfractionated heparin group | |

**Table 4: Comparison of total cost of treatment in two groups of patients studied.**

| Total cost (Rs.) | Low molecular weight heparin | | Unfraction ated heparin |
|---|---|---|---|
| | No. | % | No. |
| <1000 | 0 | 0.0 | 24 |
| 1001-2000 | 0 | 0.0 | 26 |
| 2001-3000 | 26 | 52.0 | 0 |
| 3001 & above | 24 | 48.0 | 0 |
| Total | 50 | 100.0 | 50 |
| Mean ±SD | 4183.02±1412.29 | | 993.65±418.29 |
| Inference | Total cost is significantly high in low molecular weight heparin with t=15.311' p<0.001** | | |

## CONCLUSION

From this study it was concluded that there was no significant difference in the bleeding manifestations and thrombocytopenia between low molecular weight heparin and unfractionated heparin.

Incidence of thrombocytopenia is 4% in unfractionated heparin and no thrombocytopenia in low molecular weight heparin.

There was no deviation of the treatment and there were no thrombotic complications in either group.

There was no association between thrombocytopenia and re-exposure to heparin.

The total cost in the low molecular weight heparin group was significantly higher when compared to the unfractionated heparin group and also cost per day. Per day cost for low molecular weight heparin is approximately Rs.500 and for unfractionated heparin it is Rs.100.

The main limitation of this study is:

- A small sample size, further studies with a larger sample size are required to prove the results
- Type I and Type II heparin induced thrombocytopenia could not be differentiated as it requires serology tests like serotonin assay, heparin PF4 ELISA which are not done in our laboratory.

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