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ORIGINAL ARTICLE

Use of Heparin and The Related Incidence of Heparin-Induced Thrombocytopenia in an Education and Research Hospital in Turkey

Nibal Abunahlah [1], Aisha Abimbola[2], Yildiz Okuturlar[3], Meltem Breen[1], Hakan Kocoglu[3]

[1]Clinical Pharmacy-Altinbas University,
[2]Altinbas University,
[3]Internal Medicine, Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey

Corresponding Author:
Hakan Kocoglu
Department of Internal Medicine, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey
e-mail: dr.hakankocoglu@gmail.com

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ABSTRACT

Objective: We analyzed the incidence of heparin-induced thrombocytopenia in a group of patients who received heparin (LMWH, UFH) in an education and research hospital using the 4T test score as a diagnostic tool.

Patients and Methods: A retrospective descriptive study analyzing patients using heparin preparations within the years 2015 and 2016. The risk for heparin-induced thrombocytopenia was calculated using the 4T test score system and also the monitoring of platelet counts of each patient.

Results: Of 19.257 patients who used either UFH or LMWH and were admitted to the hospital within 2015 and 2016, 308 patients were suspected to have thrombocytopenia based on their individual platelet counts by excluding only patients with thrombocytopenia. 100 patients were determined to probably have heparin-induced thrombocytopenia and were further evaluated using the 4t test score. Overall risk was calculated to be 0.5%. Incidence was calculated to be 0.15% (29 out of 19257). For patients with high-risk scores, the incidence was 0.01% (2 out of 19257). Patients who had a high 4T test score were using ranitidine. In 29 patients who had intermediate and high-risk probability for HIT, mean starting day of HIT was 6.24±3.68 days; mean withdrawal day of heparin was 9,55±5,86 days and mean delay of heparin withdrawal was 3.31±3.39 days.

Conclusion: Although the use of LMWH is being favored in the hospital when compared to UFH, health care practitioners should still remain vigilant about the occurrence of HIT as a complication of heparin therapy in hospitalized patients most especially within the first few weeks following heparin administration.

Key words: Heparin, thrombocytopenia, hospital setting, incidence

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a transient immune-mediated adverse drug reaction characterized by a decrease in platelets count greater than 50 % in patients receiving heparin preparations in the hospital due to the recognition of platelet factor 4 complexes bound to heparin by heparin-dependent platelet activating IgG antibodies [1,2]. The platelet count usually falls about 5 – 10 days after the initiation of heparin therapy [3]. However, for patients who have undergone a major surgery, the timing of heparin-induced thrombocytopenia resets to begin after the surgery [3]. Another exception includes patients who have received any heparin preparation within the past 90 days [3]. In such patients, the presence of circulating anti - platelet 4 heparin antibodies can cause an abrupt fall in platelet counts after the initiation of heparin therapy [3]. Unlike other types of thrombocytopenia that are usually associated with bleeding, heparin-induced thrombocytopenia is characterized by the development of thrombosis with moderate thrombocytopenia in most cases [4].

HIT is a transient condition as antibodies usually circulate for about 2-3 months (100

days) after which they cease to exist thus, patients with a history of HIT greater than 100 days may use heparin i.e. LMWH or UFH [2]. Upon the suspicion of HIT, all heparin preparations must be discontinued and patients should be initiated with an alternative non-heparin anticoagulant as it has been observed that up to 50% of patients who had HIT developed thrombosis later on if an alternative non-heparin anticoagulant was not initiated [5, 6]. The initiation of an alternative non-heparin anticoagulant must not be delayed as the consequences of the development of thrombosis due to the hypercoagulable state may cause pulmonary embolism, stroke, and amputation or may even lead to death. Patients with a pre-test score indicating a low probability of HIT may not need to discontinue heparin therapy [7]. In contrast, patients with an intermediate or high pre-test score should discontinue heparin therapy and should have laboratory test confirming or excluding HIT while promptly initiating an alternative anticoagulant therapy [7].

Physicians should be alert to HIT, especially in hospitalized patients, and should go to alternative treatments for heparin preparations in all patients with HIT. Considering the prevalence of HIT as a complication of drug therapy in patients using heparin (UFH, LMWH) in the hospital, the study aimed to analyze the incidence of heparin-induced thrombocytopenia in a group of patients who received heparin (LMWH, UFH) in a hospital using the 4T test score as a diagnostic tool.

PATIENTS AND METHODS

Ethical Approval

The study gained ethical approval by Marmara University's ethical committee and an official letter of request from Istanbul Bakirkoy region public hospitals association general secretariat

Study design

A retrospective descriptive study analyzing patients using heparin preparations within the years 2015 and 2016. Patients eligible for the study were receiving prophylactic or treatment doses of unfractioned heparin or low molecular weight heparin. Patients younger than 10 and incomplete medical history were excluded from the study. A complete medical history of the patients was analyzed by checking the medications the patients was using, the patient's diagnosis, platelet counts, laboratory results and medical history were also collected. The risk for heparin-induced thrombocytopenia was calculated using the 4T test score system and also the monitoring of platelet counts of each patient. Patients were evaluated based on the magnitude of platelet count fall i.e. a platelet fall between 30 – 50%, greater than 50% or less than 30% from the baseline, the timing of platelet fall count from the initiation of heparin therapy, the diagnosis of the patients and presence of other factors capable of inducing thrombocytopenia like sepsis, chemotherapy, other drugs capable of causing thrombocytopenia, acute renal failure, etc.

Heparin-induced thrombocytopenia diagnosis and evaluation

Platelet counts on day 0, day3 and days 5 – 10 were noted. Afterward, they were evaluated with the use of the 4T test scoring system. The scoring system took into consideration the presence of other things capable of causing thrombocytopenia making it unnecessary to completely exclude patients that fell under these categories because it had an impact in the final 4T score of each patient. A score of 6 – 8 indicates a high probability of heparin-induced thrombocytopenia, 4 – 5 an intermediate probability of HIT and 0-3 a low probability of HIT. Further laboratory testing like the C-SRA test and ELISA test were not included in this study because it was a retrospective study and the medical history of the patients did not indicate whether any of these tests was carried out. While using the scoring system, patients with sepsis, patients undergoing chemotherapy, patients with pancytopenia and patients who were already diagnosed with thrombocytopenia excluding heparin as the cause were categorized under patients with definite cause of thrombocytopenia while patients using drugs that can induce thrombocytopenia like ranitidine, vancomycin were categorized under possible causes of thrombocytopenia as their relative incidence of inducing thrombocytopenia is very low. Age, gender, and heparin type did not include in the criteria for the evaluation of the 4t test score. The 4T scoring system is the most evaluated pretest scoring system for HIT [5]. It uses four clinical features of HIT (thrombocytopenia, the timing of thrombocytopenia onset, thrombosis, other causes of thrombocytopenia) to analyze the probability of HIT [5, 6]. The 4t test scoring system was used because it was the only available diagnostic tool that could be used for this retrospective study as the medical history of the patients did not include the diagnosis of heparin-induced thrombocytopenia because it is considered as an adverse drug reaction.

Statistical Analysis

Number of drug related problems were presented in n (%). Confidence interval at 95% and p value < 0.005 and were considered significant. Pearson Correlation were used to study the relation between patient variables and 4T Score. For all statistical analysis, SPSS 20.0 Statistical software was used.

RESULTS

Of 19,257 patients who used either UFH or LMWH and were admitted to the hospital within 2015 and 2016, 308 patients were suspected to have thrombocytopenia based on their individual platelet counts by excluding only patients with thrombocytopenia. Each of these 308 patients was evaluated individually to check for patients with a probability of heparin-induced thrombocytopenia. 100 patients were determined to probably have heparin-induced thrombocytopenia and were further evaluated to check their risk of heparin-induced thrombocytopenia using the 4t test score. The determination of the 100 patients was based on the magnitude

of the platelet fall count i.e. ≥ 30% and the timing of platelet count fall (1-3 days, 4 -10 days, and ≥10 days).

Demographics and Variables

Out of the 100 patients suspected to have HIT, 60% used enoxaparin sodium, 16% used heparin sodium and 24% used both enoxaparin sodium and heparin alternatively. Of patients, 57% were male and 43% were female and 53% used prophylactic doses while 47% used therapeutic doses. The mean age was 58.12±21.348 years. 16% of the patients were diagnosed with cancer. 44% of patients received therapy for less than 7 days, 35% received therapy between 7-14 days and 21% received therapy for more than 14 days. Demographic variables of the study population shown in Table 1.

47% of the patients had a platelet fall within the first 72 hours, 28% had a fall in platelet count between 4 – 10 days while 25% had a fall in platelet count after 10 days. After calculating the 4T score of each patient suspected to have heparin-induced thrombocytopenia, 71% had a low probability of heparin-induced thrombocytopenia, 27% had an intermediate probability of heparin-induced thrombocytopenia and 2% had a high probability of heparin-induced thrombocytopenia.

In this study, the incidence of heparin-induced thrombocytopenia can be divided into three categories based on their risk outcome. A total of 100 out of 19257 patients were suspected to have heparin-induced thrombocytopenia, so the overall risk was calculated to be 0.5%. In regards to patients with intermediate and high-risk probability for HIT, the incidence was calculated to be 0.15% (29 out of 19257). For patients with high-risk scores, the incidence was 0.01% (2 out of 19257).

Table 1. Demographic variables of the study population

Variables	Values
No. Of patients who received heparin preparations	**19257**
No. Of patients with suspected thrombocytopenia	308
No. Of patients with suspected heparin-induced thrombocytopenia (platelets fall greater than 30% from the baseline)	100
Age, y, mean± SD	58.12 ±21.348
Gender, no.Male, no. Female	57/43
Cancer,no.(%)	16(16%)
Indication for Heparin Prophylaxis Treatment	 53(53) 47(47)
Type of Heparin Preparation Enoxaparin UFH Shift between enoxaparin and heparin	 60(60%) 16(16%) 24(24%)
Duration of treatment Less than 7 days Between 7-14 days More than 14 days	 44(44%) 35(35%) 21(21%)

Table 2. The characteristics of patients with an intermediate to high 4T test score

Patient no	Age	Gender	Time since exposure	Drug	Time to suspected HIT	4t test score	Cancer
1	66	Female	18	Enoxaparin	6	5	No
2	76	Female	4	Enoxaparin	4	4	No
3	32	Male	12	Enoxaparin	10	5	No
4	70	Male	12	Enoxaparin	5	5	No
5	75	Male	3	Enoxaparin	3	4	No
6	65	Female	6	Enoxaparin	3	4	No
7	81	Male	11	Enoxapain	4	4	No
8	84	Male	9	Enoxaparin	7	6	Yes
9	32	Female	11	Enoxaparin/ heparin	8	4	No
10	83	Female	10	Enoxaparin	7	5	No
11	58	Male	24	Enoxaparin	16	4	No
12	53	Male	2	Heparin	2	4	No
13	75	Female	18	Enoxaparin	12	4	No
14	74	Female	7	Enoxaparin	4	4	No
15	92	Female	2	Enoxaparin	2	5	No
16	19	Female	5	Heparin	5	4	No
17	67	Female	25	Enoxaparin/ heparin	16	4	Yes
18	86	Female	8	Enoxaparin	7	6	No
19	74	Female	11	Enoxaparin	3	5	No
20	62	Female	3	Enoxaparin/ heparin	3	4	No
21	85	Female	8	Enoxaparin	4	4	No
22	21	Female	9	Enoxaparin/ heparin	9	5	No
23	87	Male	3	Enoxaparin/ heparin	3	4	No
24	45	Male	9	Enoxaparin	6	5	No
25	73	Female	11	Enoxaparin	8	4	Yes
26	45	Female	13	Enoxaparin	5	4	No
27	44	Male	5	Enoxaparin/ heparin	4	4	No
28	87	Female	9	Enoxaparin	9	4	No
29	66	Female	9	Enoxaparin	6	4	yes

There was a correlation between gender and the 4t test score (r =0.267, P<0.005). It also showed a correlation between age and the 4t test score (r = 0.229, P<0.005) and correlation between a fall in platelet counts within the first 72 hours was observed (r= 0.460, p<0.001) and platelet fall within 4-10 days and the 4T test score (r = -0.656, p<0.001) There was no correlation between the duration of hospital stay, type of heparin preparation used, other drugs capable of causing thrombocytopenia, therapeutic or prophylactic doses of heparin, duration of heparin therapy and the 4t test score. However, it was observed that patients who

stayed for longer than 7 days in the hospital fell more into the intermediate and high-risk category. It was also observed that both patients who had a high 4T test score were using ranitidine. The characteristics of patients with moderate and high 4T score shown in Table 2. The distribution of the 4T test score among gender and the distribution of the 4T test score within the hospitalization days of patients were shown in Figure 1 and 2, respectively.

In 29 patients who had intermediate and high-risk probability for HIT, mean starting day of HIT was 6,24±3,68 days; mean withdrawal day of heparin was 9,55±5,86 days and mean delay of heparin withdrawal was 3,31±3,39 days. Distribution of delays of heparin withdrawal in 29 patients was shown in Figure 3.

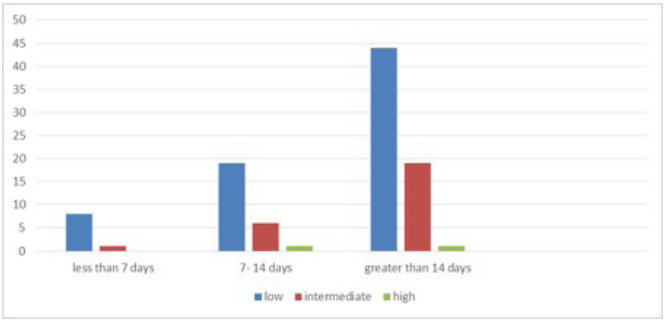

Figure 1. A chart showing the distribution of the 4T test score among gender

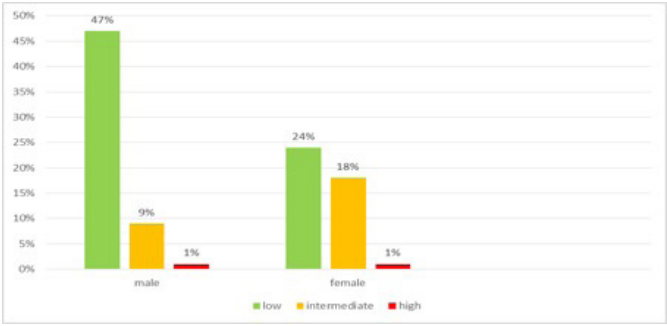

Figure 2. The chart showing the distribution of the 4T test score within the hospitalization days of patients

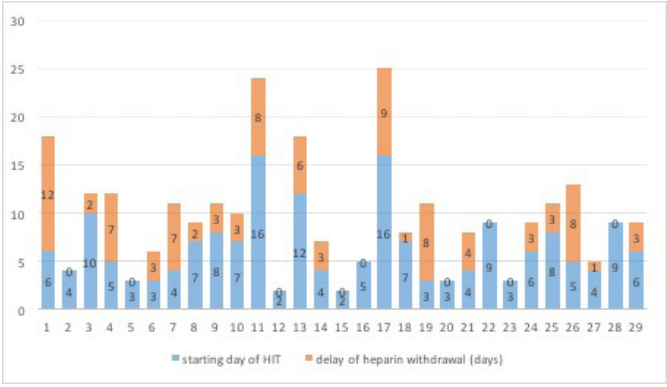

Figure 3. A chart showing the distribution of delays of heparin withdrawal in 29 patients

DISCUSSION

In this study, the use of heparins and the incidence of heparin-induced thrombocytopenia was analyzed in Bakirkoy Dr. Sadi Konuk Education and Research Hospital located in Istanbul, Turkey. In this study, it was observed from the 100 patients who were suspected to have heparin-induced thrombocytopenia that majority of the patients admitted to the hospital were administered low molecular weight heparin in preference to unfractioned heparin. This is remarkable as it shows the conscious efforts of physicians to minimize the risk of complications associated with the administration of heparin preparations most especially unfractioned heparin. Amongst the 100 patients suspected to have HIT in this study, 60% of the patients were using low molecular weight heparin and only 16% percent were using UFH. The remaining patients had shifted between the use of low molecular weight heparin and unfractioned heparin most likely due to a forthcoming surgery or other circumstances. This shows that LMWH is more frequently used in the hospital than UFH. Nevertheless, the risk of heparin-induced thrombocytopenia and its related thrombosis still bears a significant burden with the use of heparins.

In this study, the incidence of heparin-induced thrombocytopenia can be divided into three categories based on their risk outcome. A total of 100 out of 19257 patients were suspected to have heparin-induced thrombocytopenia, so the overall risk was calculated to be 0.5%. In regards to patients with intermediate and high-risk probability for HIT, the incidence was calculated to be 0.15% (29 out of 19257). For patients with high-risk scores, the incidence was 0.01% (2 out of 19257). The reason why the risk of heparin-induced thrombocytopenia was divided into three categories is due to the lack of laboratory assays to specify the exact number of patients with heparin-induced thrombocytopenia. Some studies report cases of HIT in patients that fall within the low-risk group using the 4T test score, however, the frequency is very low and that is why the 4T test score has been attributed to having a high negative predictive value. Gruel et al. [8] stated in their study that 4T test has a high negative predictive value and variable positive predictive value. A significant amount of HIT cases has been observed within the intermediate and high-risk group so for simplicity, the main incidence of heparin-induced thrombocytopenia in this study is calculated as approximately 0.15%.

In a meta-analysis carried out by Martel et al. [9] the absolute risk for HIT in patients receiving LMWH was found to be 0.2% and 2.6% in patients receiving UFH. In this study, the main incidence of heparin-induced thrombocytopenia was found to be 0.15%. However, it should be noted that there was no distinguishing between the incidence of heparin-induced thrombocytopenia in patients taking unfractioned heparin and low molecular weight heparin in this study as the data was extracted collectively and no distinctions were made between the two formulations while calculating the risk of heparin-induced thrombocytopenia when using the 4T test score. Therefore, the outcome of the incidence

of heparin-induced thrombocytopenia in this study may be attributed to the dominance of low molecular weight heparin use over unfractioned heparin use among patients evaluated in the study. It was also observed that the two patients who had a high risk of heparin-induced thrombocytopenia in this study were using low molecular weight heparin.

A significant correlation was observed between age and the 4T test score (p-value = 0.046). Patients above the age of 69 dominated the population distribution of the patients suspected to have heparin-induced thrombocytopenia. The 2 patients who had a high risk of HIT were both above the age of 80. In a retrospective study carried out by Greinache et al. [1] HIT occurs more in elderly patients greater than 60 years than in younger patients. Generally, older patients are at a higher risk for drug-related problems and adverse drug reactions. In respect to these observations, the use of heparins should be monitored closely in the elderly patients due to the higher prevalence of heparin-induced thrombocytopenia in such patients as a complication of therapy.

The two patients who had a high 4T test score were both taking ranitidine. Ranitidine has been known in case reports to induce thrombocytopenia however the incidence of thrombocytopenia related to ranitidine use is very rare. Three mechanisms have been proposed for the development of thrombocytopenia in patients which are immune mediated, allergic reactions or generalized pancytopenia [10]. In these patients who had a high 4T test score, it should be noted that the use of ranitidine might have contributed to the development of thrombocytopenia in such patients giving the benefit of the doubt. Heparins have been implicated more in the development of immune-mediated thrombocytopenia. Due to this uncertainty, more research and studies still needs to be done in the area of drug-related thrombocytopenia, its pathogenesis, and management. There is a need for the ability to identify specifically the mechanisms by which drugs like ranitidine can cause thrombocytopenia or if they have any connection to the development of other forms of thrombocytopenia for instance, in this case, heparin-induced thrombocytopenia.

The gold standard for the diagnosis of heparin-induced thrombocytopenia is the c-serotonin release assay however due to its high cost and inability to get results as quickly as possible, many hospitals rely on the Elisa test and the physician's assessment to detect heparin-induced thrombocytopenia. There is a need for the development of a faster and very efficient laboratory tool to help in the detection of heparin-induced thrombocytopenia so that the cost, duration of hospital stay as well as the morbidity and mortality of heparin-induced thrombocytopenia can be reduced significantly.

The duration of hospital stay of hospital stay had no significant correlation with the 4T test score, however, it was observed through cross tabulation tests that the patients that stayed longer in the hospital fell more into the intermediate and high-risk group of patients with heparin-induced thrombocytopenia. This observation is expected because usually, the longer patients are hospitalized, there is a higher demand for increased prophylaxis against venous thromboembolism most especially for bedridden patients and patients who are at a high risk of developing venous thromboembolism.

Limitations of this study include the lack of laboratory confirmation with functional assays and immunoassays. Therefore the results are simply based on judgments from the platelet count falls and the 4T test score. As mentioned earlier, the gold standard for the diagnosis of HIT is the c- serotonin release assays due it's high specificity and high sensitivity.

To the best of our knowledge this is the first study that shows HIT incidence in pooled patients in a Turkish Hospital which is consisted of more than 15 inpatients clinics.

In conclusion, more emphasis and observation has to be done in the surveillance of HIT in patients receiving UFH or LMWH in the hospital most especially among the elderly population. Although the use of LMWH is being favored in the hospital when compared to UFH, health care practitioners should still remain vigilant about the occurrence of HIT as a complication of heparin therapy in hospitalized patients most especially within the first few weeks following heparin administration.

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