

Original Article



Incidence of Thrombocytopenia After Enoxaparin and Heparin Taking in Hospitalized Patients

Fatemeh Amiri¹, Narges Gomar², Tahereh Abbasi Garavand^{3*}, Alireza Goodarzi¹, Narges Mohammadi Parsa⁴

¹Department of Medical Laboratory Sciences, School of Paramedicine, Hamadan University of Medical Sciences, Hamadan, Iran

²Medical Student, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

³Urology and Nephrology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

⁴Clinical Research Development Unit of Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran

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*Corresponding author:

Tahereh Abbasi Garavand,
Email: t.abbasi@umsha.ac.ir

Abstract

Background: Heparin is the most common administered anticoagulant in hospitalized patients. Thrombocytopenia can occur after heparin s administered in these patients. This study was conducted to determine the incidence of thrombocytopenia in patients treated with heparin and their clinical outcomes.

Methods: In this descriptive cross-sectional study, 754 patients admitted to Shahid Beheshti Hospital in Hamadan, Iran, who were treated with heparin were examined for the incidence of thrombocytopenia during 2022-2023. Data were extracted from the medical records of the patients and analyzed using SPSS software version 26.

Results: Among the patients, 50.4% were male, and 49.6% were female. The mean and standard deviation of the age of the patients were 63.12 ± 16.82 years. Platelet counts before and after heparin administration were 244.75 ± 79.64 and $207.66 \pm 83.39 \times 10^3/\mu\text{L}$, respectively. The frequency of thrombocytopenia in patients was 25.5%. The incidence of thrombocytopenia was 29.5% and 21.4% in men and women, respectively ($P=0.011$), and 19.3% and 28.1% of patients received enoxaparin and heparin, respectively ($P=0.010$). The mean age of patients with thrombocytopenia was 67.25 ± 15.10 years compared to 61.61 ± 17.17 years for those without thrombocytopenia ($P<0.001$). Furthermore, the length of stay in the hospital for patients with and without thrombocytopenia was 36.12 ± 52.16 and 20.9 ± 6.45 days, respectively ($P=0.015$). Moreover, the mortality rate was 35.34% and 10% in patients with and without thrombocytopenia, respectively ($P<0.001$).

Conclusion: About a quarter of patients developed thrombocytopenia within 72 hours after receiving heparin. A significant relationship was observed between thrombocytopenia incidence and older age, female gender, and heparin use. Additionally, thrombocytopenia was significantly associated with increased hospital stay duration and higher mortality.

Keywords: Heparin, Thrombocytopenia, Enoxaparin, Mortality, Length of hospital stay



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Introduction

Thrombocytopenia refers to a platelet count of less than $150\,000/\mu\text{L}$, resulting from decreased platelet production, increased platelet destruction, platelet sequestration in the spleen, and/ or a combination of both mechanisms (1). This disorder is a common hematological abnormality with clinical findings such as petechiae, purpura, bleeding, hematoma, hematuria, and the like in patients, which is mild, moderate, severe, or very severe (1,2). It has been associated with a decrease in the survival of patients in the intensive care unit (ICU) (2,3).

Different types of heparin, including unfractionated

heparin (UFH) and low molecular weight heparin (LMWH) are used as therapeutic and/or prophylaxis interventions in patients. Although enoxaparin is a widely administered LMWH with good predictable anticoagulation potential without the need for monitoring (4-6), thrombocytopenia remains one of the significant side effects of heparin therapy. It is identified as a platelet count below $150\,000/\mu\text{L}$ or a platelet count drop of about 50% or more from baseline pre-heparin platelet count (4,7). The rate of thrombocytopenia is higher in UFH compared to LMWH (6,7).

Heparin-induced thrombocytopenia (HIT) and its



mechanisms are described in the literature (4,5,8,9). HIT is a dangerous and well-documented side effect of heparin therapy, leading to platelet activation and increased risk of thrombosis and death (5). There are two types of HIT: Type I HIT is a non-antibody mediated mild form in which the symptoms and severity of thrombocytopenia typically occur 24 hours after heparin administration (6). Type II HIT is the most significant non-bleeding clinical complication of heparin and is caused by the production of antibodies against the heparin-platelet factor 4 (PF4) complex. It is a life-threatening condition, occurring in 1 to 5% of heparin-receiving patients (7). Type II HIT is diagnosed based on the 4Ts clinical assessment scoring and the HPF4 antibody assay (7-10). Some cases of thrombocytopenia related to heparin administration have unknown reasons or depend on other factors and are not classified as HIT. Heparin is associated with thrombocytopenia in hospitalized patients in the ICU. In addition, spontaneous thrombocytopenia also occurs in a significant number of hospitalized patients and may be intensified by heparin administration (11). Therefore, this issue requires accurate and timely diagnosis. It can also affect the clinical outcome of the patient. Considering the widespread use of heparin, especially in hospitalized patients, this study sought to investigate the prevalence of thrombocytopenia in heparin-received hospitalized patients at Shahid Beheshti Hospital in Hamadan, regardless of 4Ts clinical assessment scoring and the HPF4 antibody assay. It also evaluated the association between thrombocytopenia and the clinical outcomes of the patients.

Materials and Methods

This cross-sectional study comprised all patients admitted to Shahid Beheshti Hospital in Hamadan during 2022-2023 who had been administered heparin. Inclusion criteria were hospitalization, heparin administration, thrombocytopenia, and the availability of pre- and post-heparin administration platelet counts. Exclusion criteria included a history of coagulopathy, history of thrombocytopenia, blood diseases, chemotherapy, or absence of platelet counts in the patient's medical records. Data were extracted from patient medical records using a checklist that included the following information: demographic information (age and gender), pre-heparin platelet count, post-heparin platelet count, type of administered heparin (UFH or LMWH enoxaparin), reason for heparin administration (therapeutic or prophylaxis), length of hospital stay, and final outcome (mortality or discharge). After data extraction, data analysis was performed using SPSS version 26. The data were described using descriptive statistics to express the mean and standard deviation for quantitative variables and the ratio and percentage for qualitative variables. Additionally, the Mann-Whitney non-parametric test and the Chi-square test were used to compare findings, with a significance level set at less than 0.05.

Results

The mean age of the patients was 63.12 ± 16.82 years. In terms of gender, 380 (50.4%) were men, and 374 (49.6%) were women. The mean and standard deviation of platelet count before and after heparin administration were 244.75 ± 79.64 and $207.66 \pm 83.39 \times 10^3/\mu\text{L}$, respectively. Thrombocytopenia occurred in 192 patients (25.5%). Table 1 shows the reasons for patient hospitalization.

Table 2 presents the frequency of the type and reason for heparin administration, as well as the hospitalization outcomes of the patients. According to the findings, 30.2% of patients received enoxaparin, and 69.6% received heparin. The reasons for heparin administration were as follows: 67.4% for prophylaxis and 32.6% for treatment. In terms of hospitalization outcomes, 83.6% of patients were discharged, and 16.4% were died.

Table 3 shows the frequency of thrombocytopenia in the patients based on the type of heparin, the reason for heparin administration, as well as the outcome of hospitalization.

Based on the presented findings in Table 3, the incidence of thrombocytopenia in patients receiving enoxaparin was significantly lower than that of patients receiving heparin ($P=0.011$). Additionally, the mortality rate in thrombocytopenic patients was significantly higher than non-thrombocytopenic ones ($P<0.001$). However, no significant relationship was observed between the reason for heparin administration and the incidence of thrombocytopenia.

The mean and standard deviation of the age of patients with and without thrombocytopenia were 67.25 ± 15.10 and 61.61 ± 17.17 years, respectively. According to the non-parametric Mann-Whitney test, there was a significant difference in age between patients with and without thrombocytopenia ($P<0.001$), as presented in Figure 1.

The mean and standard deviation of hospital stay days of patients with or without thrombocytopenia were 16.36 ± 12.52 and 9.45 ± 6.20 days, respectively. Additionally, a significant difference was observed between patients with or without thrombocytopenia in terms of length of hospital stay ($P=0.015$), as indicated in Figure 2.

The effect of gender on the incidence of thrombocytopenia was also evaluated. The results are presented in Table 4.

As observed in Table 4, a significant difference was observed between the gender of heparin-receiving patients and the incidence of thrombocytopenia ($P=0.011$), and the incidence of thrombocytopenia was higher in the men than in the women.

Discussion

Considering the significance of thrombocytopenia, this study aimed to determine the relationship between thrombocytopenia and heparin consumption in patients admitted to Shahid Beheshti Hospital in Hamadan

Table 1. The Frequency of Reasons for Hospitalization of Heparin-Receiving Patients

Cause of Hospitalization	Number	Percent	Cause of Hospitalization	Number	Percent
Abdominal pain	14	1.9	Hepatitis	4	0.5
Acute nephritis	4	0.5	Heart failure	16	2.1
Acute pancreatitis	4	0.5	Hypertension	4	0.5
Acute renal failure	26	3.4	Hyperkalemia	4	0.5
AF pleural effusion	4	0.5	Hypoglycemia	15	2.0
Asthma	4	0.5	Irritable bowel syndrome	4	0.5
Bladder stone	8	1.1	Installing devices in the urinary system	4	0.5
BPH	8	1.1	Intestinal disorder	7	0.9
Cellulitis	10	1.3	Kidney stone	4	0.5
Chest pain	3	0.4	Lupus	4	0.5
CKD	26	3.4	Lupus DVT	7	0.9
CKD DVT	4	0.5	MI	22	2.9
Colitis	3	0.4	Nephritis	4	0.5
COPD	42	5.6	Nephritic syndrome	4	0.5
COVID-19	22	2.9	Opioid toxicity	4	0.5
Diabetic foot ulcer	7	0.9	Pancreatitis	11	1.5
DKA	23	3.1	Pneumonia	90	11.9
Diabetes mellitus	3	0.4	Polycystic kidney	4	0.5
DVT	46	6.1	Port vein thrombosis	4	0.5
DVT MI	4	0.5	PTE	80	10.6
DVT PTE	15	2.0	PTE DVT	4	0.5
Encephalitis	3	0.4	Rheumatoid arthritis	28	3.7
Gallstone	4	0.5	Scleroderma	4	0.5
Gastroenteritis	4	0.5	Scleroderma hypertension	8	1.1
Gastrointestinal bleeding	10	1.3	Sepsis	27	3.6
Septic shock	4	0.5	Urethritis	4	0.5
Stomach cancer	7	0.9	UTI	31	4.1
Systemic sclerosis	10	1.3	UTI MI	3	0.4
Tuberculosis	8	1.1	UTI sepsis	4	0.5
Thrombophlebitis	4	0.5	Total	754	100.0
Ulcerative colitis	7	0.9			

Note. AF: Atrial fibrillation; BPH: Benign prostatic hyperplasia; CKD: Chronic kidney disease; DVT: Deep vein thrombosis; MI: Myocardial infarction; IBS: Irritable bowel syndrome; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus Disease 2019; DKA: Diabetic ketoacidosis; PTE: Pulmonary thromboembolism; UTI: Urinary tract infection.

Table 2. Heparin Type, Reasons for Heparin Administration, and Hospitalization Outcomes

Variable	Number	Percent
Type of heparin		
Enoxaparin	228	30.2
Heparin	526	69.6
Total	754	100
Reasons for heparin administration		
Prophylaxis	508	67.4
Treatment	246	32.6
Total	754	100
Clinical outcomes		
Discharge	630	83.6
Death	124	16.4
Total	754	100

Table 3. Frequency of Thrombocytopenia According to Heparin Type, Reasons for Heparin Administration, and Hospitalization Outcomes

Variable	Incidence of Thrombocytopenia		P Value*
	Yes	No	
Type of heparin			
Enoxaparin	44 (19.3)	184 (80.7)	0.011
Heparin	148 (28.1)	378 (71.9)	
Reasons for heparin administration			
Prophylaxis	127 (25)	381 (75)	0.674
Treatment	65 (26.4)	181 (73.6)	
Clinical outcomes			
Discharge	124 (64.6)	506 (90)	<0.001
Death	68 (35.4)	56 (10)	
Total	192 (100)	562 (100)	

*P value less than 0.05 and significant differences

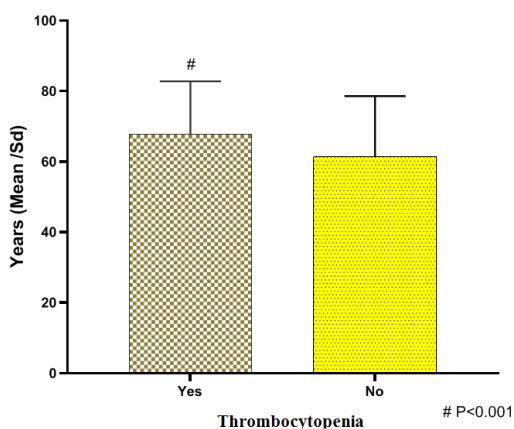


Figure 1. Mean and Standard Deviation of the Age of Heparin-receiving Patients with or Without Thrombocytopenia

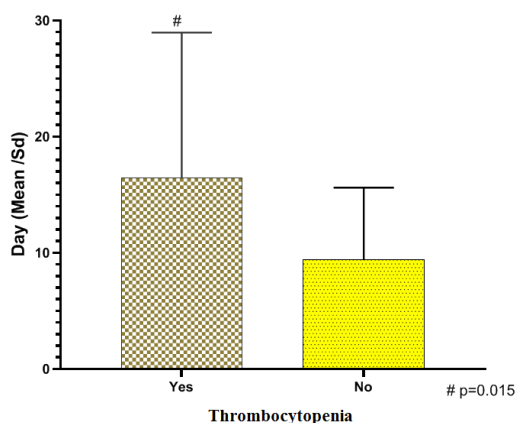


Figure 2. Mean and Standard Deviation of Hospital Stay Days in Heparin-receiving Patients With or Without Thrombocytopenia

Table 4. The Frequency of Thrombocytopenia in Heparin-receiving Patients by Gender

Thrombocytopenia	Gender		P Value*
	Men	Women	
Yes	112 (29.5)	80 (21.4)	0.011
No	268 (70.5)	294 (78.6)	
Total	380 (100)	374 (100)	

*P value less than 0.05 and significant differences

during 2022-2023. In the current study, the incidence of thrombocytopenia in heparin-receiving patients was 25.5% overall, regardless of their 4Ts clinical assessment scoring and the HPF4 antibody assay. In a study conducted by Ahmadinejad et al, the frequency of thrombocytopenia caused by heparin, based on platelet count (regardless of HPF4 antibody assay), was 15%, and 5.4% was confirmed based on Anti-PF4/heparin antibodies (12). Oliveira et al reported 36.4% thrombocytopenia in patients treated with long-term heparin (4 days or more) (13). The results of Farasatinasab and colleagues’ study indicated that the total rate of post-heparin thrombocytopenia was 31.6%, with 5.6% confirmed as HIT by enzyme-linked immunosorbent assay (ELISA) (14). The incidence of thrombocytopenia in the mentioned studies was reported to be between

15% and 36%. The high fluctuation in the incidence of thrombocytopenia following heparin consumption may be due to differences in the diagnostic method (based on platelet count, 4Ts clinical assessment, and/or anti-PF4/heparin antibody), the duration of heparin use, or the underlying diseases of the patients. Some studies reported HIT-II rates according to the American Society of Hematology (8,9), while other studies evaluated the total rate of thrombocytopenia without considering the immune type. A study by Dhakal et al revealed that cardiopulmonary bypass followed by hemodialysis is associated with a relatively high rate of thrombocytopenia. Compared with whites, blacks and other races were also more likely to develop thrombocytopenia (15). In the current study, the underlying diseases of the patients were heterogeneous and different. Therefore, it was not valid to assess the relationship between underlying diseases and thrombocytopenia incidence. In a study by Oliveira et al, a significant relationship was observed between thrombocytopenia and a longer duration of heparin treatment (13), but the exact duration of heparin therapy was not determined in the current study.

In the present study, the frequency of thrombocytopenia in heparin-receiving patients was significantly higher than in enoxaparin-receiving patients. A study conducted by Farasatinasab et al lays further support for the current study, showing that replacing heparin with rivaroxaban (another kind of LMWH) decreased the frequency of thrombocytopenia from 31.6% to 5.6% (14). However, Kim et al compared the incidence of thrombocytopenia after administering heparin or enoxaparin, finding no significant difference between the two drugs in terms of thrombocytopenia rate (16).

LMWH has many advantages over conventional heparin (UFH). Enoxaparin is an anticoagulant drug with low molecular weight, rapid effect, and long half-life. Its antiplatelet effect is greater and leads to a decrease in thrombin production and activation (4-6,17). Therefore, enoxaparin seems more effective than heparin in reducing anti-platelet antibody production and thrombocytopenia.

In the present study, the length of hospital stays and the frequency of death in heparin-receiving patients were significantly higher than in enoxaparin-receiving patients. According to Liu and colleagues’ study, heparin administration was a risk factor for severe disease and thrombocytopenia, which is associated with an increase in ICU hospitalization and mortality rate (11). Furthermore, the present study indicated that the mean age of patients with thrombocytopenia is significantly higher than that of patients without thrombocytopenia. Studies by Dhakal et al and Oliveira et al also indicated that older age increases the risk of thrombocytopenia (13,15). Likewise, Oliveira and colleagues’ study (13) reported a significant relationship between thrombocytopenia and older age which is consistent with our findings. In older age, thrombocytopenia may be related to an increase in other risk factors.

In the present study, the incidence of thrombocytopenia caused by heparin administration was significantly lower in women than in men. In the study of Warkentin and Kelton, the incidence of thrombocytopenia in women was also significantly lower than in men (18). Likewise, the study by Dhakal et al reported that women have a lower risk for thrombocytopenia (15). The results of our study are consistent with the findings of Warkentin and Kelton and Dhakal et al, showing a higher incidence of thrombocytopenia in men than in women (13,15). Moreover, according to our results, the incidence of thrombocytopenia after administering heparin was significantly higher in older patients. Similarly, Dhakal et al reported a higher thrombocytopenia rate in older patients than in younger ones (15). Host-related factors, including gender and age, are identified as risk factors that increase the thrombocytopenia rate (19,20). Other risk factors and comorbidities may also contribute to the increased thrombocytopenia in older age, requiring further investigation.

In this study, no significant relationship was observed between the reason for heparin administration (therapeutic or prophylaxis) and the occurrence of thrombocytopenia. However, thrombocytopenia was significantly associated with an increased length of hospital stay and mortality. Liu et al identified heparin administration and thrombocytopenia as risk factors for disease severity, reporting that thrombocytopenia is associated with an increase in ICU hospitalization and mortality (11). Shah et al recorded more deaths but no longer hospital stay days for HIT patients with a history of deep vein thrombosis (21). Thrombocytopenia is associated with increased mortality rate, longer hospitalization, and greater need for intensive care in hospitalized patients (4,5).

Conclusion

Approximately a quarter of heparin-receiving patients experienced thrombocytopenia. A significant relationship was observed between thrombocytopenia and older age, male gender, and heparin. Moreover, thrombocytopenia was significantly associated with an increased length of hospital stay and mortality. Due to the adverse effect of thrombocytopenia on the duration and outcome of hospitalized patients, the monitoring of platelet count is suggested.

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Authors' Contribution

Conceptualization: Tahereh Abbasi Garavand.

Data curation: Fatemeh Amiri, Narges Gomar, Tahereh Abbasi Garavand, Alireza Goodarzi, Narges Mohammadi Parsa.

Investigation: Narges Gomar, Tahereh Abbasi Garavand, Alireza Goodarzi.

Methodology: Fatemeh Amiri, Narges Gomar, Tahereh Abbasi Garavand, Alireza Goodarzi, Narges Mohammadi Parsa.

Project administration: Tahereh Abbasi Garavand.

Supervision: Tahereh Abbasi Garavand.

Validation: Tahereh Abbasi Garavand.

Writing—original draft: Fatemeh Amiri.

Writing—review & editing: Fatemeh Amiri, Tahereh Abbasi Garavand.

Competing Interests

The authors declared no potential conflict of interests with respect to the research, authorship, and/or publication of this study.

Ethical Approval

The present study was approved by the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1401.140).

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