HEMATOLOGY, TRANSFUSION AND CELL THERAPY

www.htct.com.br

Letter to the Editor

Association between time of heparin exposure and platelets decline in patients with heparin induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an immune-based side effect of heparin due tothe formation of platelet-activating antibodies, which target platelet factor 4-heparin (PF4/H) complexes and results in thrombocytopenia.[1] HIT is typified by a decline in platelet counts that typically occurs within 5 to 14 days after the initiation of heparin therapy and diagnosed based on the evaluation of clinical presentation through a validated pretest probability score, known as the 4Ts score, in combination with PF4/H antibodies corroboration which is a laboratory antigen assay.[2] Furthermore, HIT is usually seen patients receiving unfractionated heparin (UFH) and less common with low–molecular weight heparin (LMWH). In this letter, we presented longitudinal changes in the complete blood count (CBC) of confirmed HIT patients in the intensive care units (ICUs).[3]

This retrospective study was conducted on ICU patients receiving heparin at Rasoul Akram Hospital, Tehran, Iran. Patients with clinical suspicion of HIT were included if they had available PF4 test results and 4Ts score.[4] Also, individuals with preexisting heparin allergy or history of coagulopathy, autoimmune disease, and pancytopenia were excluded from the study. Linear mixed model (LMM) was used to assess longitudinal changes in mean CBC components including platelet, hemoglobin, and white blood cell (WBC).

A total of 99 suspected HIT patients were enrolled in the study and divided into positive ($n = 35$) and negative ($n = 64$) groups for PF4 antibody (Table 1). A significant difference was observed in the treatment service of patients between positive and negative PF4 groups ($p = 0.025$), and the total 4T score for positive PF4 group was notably higher than negative PF4 ($p = 0.001$). Moreover, 88.6 % of positive PF4 patients were high risk for HIT whereas 68.8 % of negative PF4 were intermediate ($p = 0.001$). Mean platelets showed a significant decrease in positive PF4 patients for both genders ($p = 0.001$) over the time of heparin therapy (3rd, 5th, 7th day) while changes in mean hemoglobin level and WBC were not significant (Table 2). Figure 1 represents changes in mean platelets for different genders (Figure 1A) and treatment services (Figure 1B) during heparin therapy in positive PF4 patients.

Age, gender, treatment service, and duration of heparin therapy were considered as covariates in LMM analysis to find their effects on longitudinal changes in CBC components. Our results showed that changes in mean platelets in surgical patients were remarkably greater than in internal patients ($\beta = -32.6$, $p = 0.03$). Moreover, duration of the patient's exposure to heparin significantly affected longitudinal changes in mean platelets in positive PF4 patients ([3rd day: $\beta = -6.13$; $p = 0.001$], [5th day: $\beta = -97.1$; $p = 0.001$], [7th day: $\beta = -112.2$; $p = 0.001$]). A significant relationship was found between changes in mean hemoglobin and gender ($\beta = -1.7$, $p = 0.005$) and treatment service ($\beta = -1.3$, $p = 0.04$) of positive PF4 patients over the time of heparin therapy. Age of patients did not affect longitudinal changes in CBC components.

The occurrence rate of HIT in patients on heparin is highly variable. HIT is commonly less frequent in patients receiving low molecular weight heparin (LMWH) (< 1 %) in comparison with UHF (1–5 %).[5] Moreover, females are more prone to develop HIT than males. Consistent with us, the rate of HIT occurrence in surgical ICU patients has been shown to be higher than in medical ICU patients.[6] In surgical patients treated with UFH, the risk of HIT is 10 to 15 times higher than in those treated with LMWH. Heparin administration prophylactically runs the risk of antibody formation, while clinical presentations observe more in patients treating with therapeutic doses. Just 5 % to 30 % of cases with the production of HIT IgG antibodies will develop HIT.[7] The main causes of thrombocytopenia in HIT patients are major surgical procedures, transfusion reactions, side effects of drugs, and sepsis. It has been recommended that monitoring of thrombotic complications in patients on heparin can be a better indicator of HIT diagnosis than uncomplicated thrombocytopenia.[8] In uncomplicated patients with low susceptibility to HIT, administration of heparin should not be stopped and additional laboratory testing is not necessary. But heparin

Table 1 – Demographic and clinical data of ICU patients in two groups of study (*n* = 99).

Patients' variables	Positive PF4 (*n* = 35)	Negative PF4 (*n* = 64)	P value
Age (year)[a]	63.94±17.51	64.06±17.80	0.974
Gender (n,%)[b]			
Male	19 (54.3)	41 (64.1)	0.341
Female	16 (45.7)	23 (35.9)	
Treatment service (n,%)[b]			
Internal patients	16 (45.7)	44 (68.7)	0.025
Surgical patients	19 (54.3)	20 (31.3)	
Type of heparin (n,%)[b]			
UHF	33 (94.3)	57 (89.1)	0.387
LMWH	2 (5.7)	7 (10.9)	
Indication for heparin (n,%)[b]			
Treatment	16 (45.7)	20 (31.3)	0.153
Prophylaxis	19 (54.3)	44 (68.8)	
Comorbidities (n,%)[b]			
Hypertension	21 (60)	27 (42.2)	0.090
Valvular heart disease	1 (2.9)	1 (1.6)	0.662
Atrial fibrillation	4 (11.4)	5 (24)	0.550
Ischemic heart disease	14 (40)	29 (45.3)	0.610
Hear failure	4 (11.4)	9 (14.1)	0.711
Diabetes	6 (17.1)	21 (32.8)	0.094
Stroke	5 (14.3)	9 (14.1)	0.976
Chronic kidney disease	4 (11.4)	17 (26.6)	0.078
COPD	5 (14.3)	7 (10.9)	0.626
Deep vein thrombosis	3 (8.6)	6 (9.4)	0.894
Pulmonary embolism	6 (17.1)	3 (4.7)	0.039
Cancer	5 (14.3)	10 (15.6)	0.859
APACHE II score [a]	7.02±15.43	4.47±11.85	0.361
SOFA score [a]	8.74±1.26	9.03±1.39	0.312
Total 4T score	6.31 ± 0.71	4.67±1.00	0.001
Low risk (n,%)	0	8 (12.5)	
Intermediate risk (n,%)	4 (11.4)	44 (68.8)	0.001
High risk (n,%)	31 (88.6)	12 (18.7)	

Abbreviations: ICU, intensive care unit; PF4, platelet factor 4; UHF, unfractionated heparin; LMWH, low molecular weight heparin; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; Sequential Organ Failure Assessment.

[a] Continuous data are presented as mean ± standard deviation.
[b] Categorical data are presented as frequency (%).

Table 2 – Complete blood count components of positive PF4 patients during heparin therapy in ICUs.

Variables*	Gender	Duration of heparin therapy				p value
		1 day	3 day	5 day	7 day	
Platelets	Male	241.89±91.10	173.47±84.46	122.42±69.94	103.0 ± 45.86	0.001
	Female	206.44±105.60	141.0 ± 69.69	123.25±56.67	113.46±59.18	0.001
Hemoglobin	Male	11.63±3.54	10.30±2.74	11.13±2.30	10.62±3.17	0.541
	Female	11.10±2.29	10.86±1.39	9.88±1.19	10.06±1.98	0.156
WBC	Male	11.46±5.08	10.62±3.61	9.21±3.61	8.76±3.65	0.147
	Female	10.71±3.39	11.66±3.49	11.31±3.85	10.80±4.34	0.650

Abbreviations: PF4, platelet factor 4; ICU, intensive care unit; WBC, weight blood cell.

* Continues data are presented as mean ± SD.

administration should be discontinued and alternative anticoagulation should be initiated in patients with an increased susceptibility to HIT.[9]

Based on the findings of this study, duration of the patient's exposure to heparin affects significantly magnitude of decline in platelets of patients with PF4/H antibody and may result in discontinuing heparin administration. Also, the degree of platelet decline in surgical HIT patients is notably greater than in internal HIT patients.

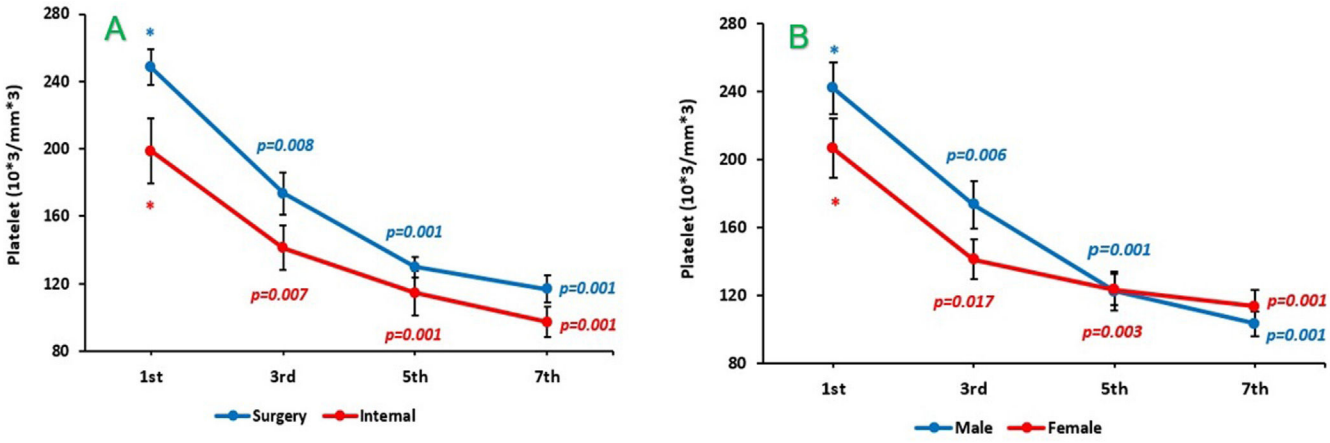

Figure 1 – Changes in mean platelets estimated by linear mixed model (LMM) analysis based on treatment services (1A) and gender (1B) during heparin therapy in confirmed heparin-induced thrombocytopenia (HIT) patients with positive platelet factor 4-heparin (PF4-H) antibody (*reference: first day).

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

This study has been approved by the local Ethics Committee (IR.IAU.KHUISF.REC.1397.152), and written informed consent was obtained from all individuals.

REFERENCES

1. Cuker A, Cines DB. How I treat heparin-induced thrombocytopenia. Blood. 2012;119(10):2209–18.
2. Warkentin TE. How I diagnose and manage HIT. Hematol Am Soc Hematol Educ Program. 2011;2011(1):143–9.
3. Warkentin TE, Sheppard J-AI, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood. 2006;108(9):2937–41.
4. Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. Blood. 2012;120(20):4160–7.
5. Warkentin TE, Cook RJ, Marder VJ, Sheppard J-AI, Moore JC, Eriksson BI, et al. Anti–platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. Blood. 2005;106(12):3791–6.
6. Linkins L-A, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2):e495S–530S.
7. Warkentin TE, Sheppard J-AI, Moore JC, Moore KM, Sigouin CS, Kelton JG. Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia: how much class do we need? J Lab Clin Med. 2005;146(6):341–6.
8. Baldwin ZK, Spitzer AL, Ng VL, Harken AH. Contemporary standards for the diagnosis and treatment of heparin-induced thrombocytopenia (HIT). Surgery. 2008;143(3):305–12.
9. Pouplard C, Gueret P, Fouassier M, Ternisien C, Trossaert M, Regina S, et al. Prospective evaluation of the '4Ts' score and particle gel immunoassay specific to heparin/PF4 for the diagnosis of heparin-induced thrombocytopenia. J Thromb Haemost. 2007;5(7):1373–9.

Omid Moradi Moghaddam [a,b], Zohreh Heydari Ramsheh [b], Mohsen Sedighi [a], Alireza Amanollahi [a], Mohammad Niakan Lahiji [a,b,*]

[a] *Trauma and Injury Research Center, Iran University of Medical Sciences, Tehran, Iran*

[b] *School of Medicine, Iran University of Medical Sciences, Tehran, Iran*

*Corresponding author at: Department of Anesthesiology and Critical Care, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

E-mail address: niyakanlahiji.m@iums.ac.ir (M.N. Lahiji).

Received 6 April 2023
Accepted 13 November 2023
Available online 19 January 2024

https://doi.org/10.1016/j.htct.2023.11.009
2531-1379/