Original Article

Frequency of Heparin-inducedthromocytopenia in Patients Treated with Un-fractionated vs. Low Molecular-weight Heparin

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Objective: To compare the frequency of heparin-induced thrombocytopenia with un-fractionated vs. low-molecular-weight heparin in patients presenting with deep vein thrombosis

Methods: This randomized control trial was conducted at department of medicine, Mayo Hospital, Lahore for 6 month i.e. 18-05-2016 to 19-11-2016. Informed consent was taken from all the patients. The non-probability, consecutive sampling technique was used. All the data was collected in terms of two groups. Group A consists of patients receiving UFH 2.5cc in 97.5cc normal saline in micro-burette @8udrops/min continuous infusion while group B consists of patients receiving LMWH (injection enoxaparin) 60mg subcutaneously twice a day. Platelet count was done on 3rd and 10th day. If platelet count is found to be <50% than baseline, then HIT was labeled. All the collected data was entered and analyzed on SPSS version 20.

Results: In our study the mean age of the patients was 52.33±7.38 years, the male to female ratio of the patients was 1.14:1. In this study the HIT was found in 9(3.75%) patients. Statistically significant difference was found between the study groups with HIT of the patients. i. e p-value=0.017.

Conclusions: HIT is an established complication of heparin therapy. Use of LMWH significantly decreases chances of HIT as compared to UFH in patients presenting with DVT in medical wards.

Keywords: heparin-induced thrombocytopenia, deep vein thrombosis, un-fractionated heparin, low-molecular-weight heparin.

Introduction

Anticoagulants are widely used in the modern era for management of thrombotic disorders like deep venous thrombosis (DVT) and pulmonary embolism.[1] Two main types of injectable anticoagulants used are un-fractionated (UFH) and low-molecular-weight heparin(LMWH).[2] LMWH has advantage of longer half-life, twice daily administration and predictable response.[3] Still UFH is widely used as the primary agent for venous thromboembolism (VTE) prophylaxis in the hospital setting due to the ease of use and insignificant cost.[4] Heparin induced thrombocyt-openia (HIT) is a well-recognized complication of both UFH and LMWH. IgG antibodies formed in response to heparin therapy form immune complexes with heparin and Platelet factor 4. These bind to Fc receptors lead to platelet activation and consequent thrombocy- topenia. It occurs in ~5% patients receiving UFH and 0.5% of those receiving LWMH.[5] Despite the apparent thrombocytopenia, half of the patients developing HIT will have thromboembolism (arterial or venous) instead of bleeding, which may further complicate the ongoing disease of the patient.[6,7,8] Cases developing HIT can develop microthrombosis if warfarin is given so recently initiated warfarin should be reversed with Vitamin-K.[9] They are given non-heparin anticoagulants like direct oral anticoagulants (argatroban, lepirudin, danaparoid), fondaparinux and in severe cases, intravenous immunoglobulin.[10,11,12]

The rationale of this study is to assess the frequency of HIT in our population and to compare it in DVT patients receiving UFH and LMWH. This will help to consolidate the findings of previous international studies.

Methods

A randomized controlled trial was carried out in Department of Medicine, Mayo Hospital, Lahore over 6 months from May to November, 2016. Sample size of 240 cases (120 cases in each group) was calculated with 80% power of test, 5% level of significance and taking expected percentage of HIT i.e. 5% in unfractionated heparin and 0% with LMWH in patients presenting with DVT. Patients aged 40-65 years irrespective of gender presenting with pain and swelling of lower limbs, assessed clinically and confirmed through ultrasonography (>50x decrease in flow in deep veins) diagnosed during previous one week and willing to participate in research were included in the study. Those with current or previous history of STEMI, partial paralysis, comorbid or previous stroke, malignancy,

chronic renal disease, baseline platelet count <150,000/µl were excluded. A written consent was taken. Demographic details and site of DVT were noted. Patients were randomly divided in two groups by using lottery method. Group A patients received UFH 2.5cc in 97.5cc normal saline in micro-burette @8udrops/min continuous infusion while group B patients received LMWH (Injection Enoxaparin) 60mg subcutaneously twice a day. Blood sample was obtained at presentation for assessment of baseline platelet count. Patients were followed up for 10 days. On 3rd and 10th day platelet count was assessed again. A patient was labeled as a case of HIT if platelet count was found to be <50% than baseline on 3rd or 10th day. Fondaparinux was given for management of HIT. All data was collected on a predesigned proforma and analyzed using SPSS version 20. Mean and standard deviation were calculated for quantitative variables like age, duration of DVT, platelet count at baseline, 3rd day and 10 day post treatment. The frequency and percentage was calculated for qualitative variables like gender, site of DVT, and HIT in both groups. Frequency of HIT was compared in both groups by using chi-square test. p-value ≤0.05 was taken as significant. Data was stratified for age, gender, platelet count (baseline), duration of DVT & site of DVT. Post-stratification, chi-square was applied with p-value ≤0.05 as significant.

Results

In our study 240 cases participated. The mean age of the patients was 52.33±7.38 years (Range 40 -65 years). Out of these there were 128 males (53.33%) and 112(46.67%) females. The male to female ratio was 1.14:1. Patients were divided into two groups A and B. Mean age of group A patients was 52.60±7.20 years while in group B it was 52.28±7.58 years. Group A had 72 males and 48 females while group B had 56 males and 64 females. 121 cases presented with DVT of left lower limb whereas right lower limb DVT was seen in 119 cases. Mean duration of DVT in group A was 2.38±1.124 weeks while it was 2.59±1.096 weeks in group B. Stratification on the basis of age, gender and side of involvement gave statistically insignificant results. **(Table-1)** Mean baseline, 3rd and 10th days platelet counts (x10^9 /l), in group A were 324.24±43.12, 291.68±42.06, and 230.75±44.44 , while in group B these were 317.00±44, 283.73±44.50 and 238.21±51.28 respectively. **(Table-2)** HIT developed in 9(3.75%) patients. (**Fig-I)** These 8 were from group A and 1 from group B. Statistically significant difference was seen between the two groups. (p-value=0.017). **(Table 3)** The study results showed that in 5 cases of HIT (all group A) had ≤2 weeks duration of DVT while 4 cases (3 and 1 from group A and B respectively) had >2 weeks duration of DVT. Stratification amongst the two groups by duration of DVT also gave statistically insignificant results, i.e. p-value=0.061 & 0.334 respectively.

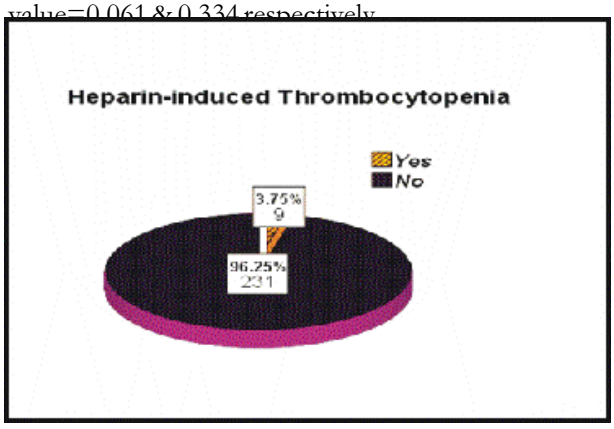

Fig-1: Frequency distribution of HIT (n=240).

Table-2: Comparison of platelets count within study groups.

Platelet count (x10^3/ul)	Mean ±SD Group A (n=120)	Group B (n=120)
Baseline	324.24±43.12	317.00±44.00
3rd day	291.68±42.06	283.73±44.5
10th Day	230.75±44.44	238.21±51.28

Table-3: Comparison of HIT cases within study groups

	Group A (n=120)	Group B (n=120)
No. of Cases	08	01
p-value	0.017	
Chi value	5.65	

Discussion

HIT is an adverse drug reaction presenting as a prothrombotic disorder related to antibody-mediated platelet activation. LMWH has been largely replacing UFH as front-line therapy because it is judged to be at least as efficacious in preventing thromboembolic complications and to cause fewer bleeding adverse outcomes. However, similar efficacy and risks have been described. The incidence of HIT is approximately ten fold higher with UFH (~5%) than with LMWH (0.5%) in surgical patients treated with prophylactic doses.[5] This study was a randomized control trial in which the patient was blinded to the type of heparin used. The frequency of HIT is

Table-1: Comparison of demographic data among study groups .

Variables		HIT	Group A	Group B	Total	p-value
Age (Years)	=50	Present	04	01	05	0.363
		Absent	49	50	99	
	>50	Present	04	0	04	0.056
		Absent	63	69	132	
Gender	Male	Present	05	01	06	0.230
		Absent	67	55	122	
	Female	Present	03	0	03	0.076
		Absent	45	64	109	
Lower limb involved	Left	Present	04	01	05	0.2
		Absent	55	61	116	
	Right	Present	04	0	04	0.119
		Absent	57	58	115	

context in which heparin is administered. In our study HIT developed in 8 patients receiving UFH and 1 receiving LMWH. (p value=0.012). A study by Junqueira DR, et al pooled analysis showed statistically significant reduction in the risk of HIT with LMWH compared with UFH (risk ratio (RR) 0.24, 95% confidence interval(CI) 0.07 to 0.82; P = 0.02) which suggests that if given LMWH patients would have 76% less probability of developing HIT compared with UFH. [13] Van Matre ET, et al found in their study that HIT occurred in 0.19% patients who received UFH and in 0.06% of patients who received LMWH.[14] Menon H, et al in their study reviewed cases that were tested for HIT and established that the use of enoxaparin (LMWH) was associated with a significantly less frequent testing and hence cost saving over intravenous UFH when used for therapeutic anticoagulation, but this cost saving was not observed for prophylactic anticoagulation.[4] Another study provided a rigorous analysis of Heparin-PF4 antibodies in patients treated for DVT with LMWH vs. UFH. In this study, Heparin-PF4 antibodies (measured by a commercial ELISA method) developed in 9.1% of patents in the UFH group vs. 2.8% of patients in the LMWH group (both treated for 57 days).[15] In a randomized, double blind study Lubenow N, et al reported that HIT developed in 0.8% cases trauma patients managed with LMWH and 4% cases managed with UFH. They also observed that severity of trauma and need for major surgery influenced the development of HIT.[16] A meta-analysis of 5 randomized or prospective nonrandomized trials mostly of orthopedic surgery by Martel N et al indicated a risk of 2.6% (95% CI, 1.5%3.8%) for UFH and 0.2% (95% CI, 0.1%0.4%) for LMWH.[17] In a meta-analysis by Warkentin et al, HIT was higher in UFH group as compared to LMWH, risk was higher in surgical patients as compared to medical patients.[18] Another study reported that with UFH, 0.53% cases developed HIT while no (0%) patient receiving LMWH had HIT and the difference was insignificant (P=0.05).[15] A retrospective cohort study involving 333 acute care facilities from USA concluded that LMWH and UFH are equally effective in prevention of thromboembolism but LMWH is associated with fewer complications.[19] In our study HIT was seen in 3 females and 5 males in group A and only patient in group B was a male. The difference was statistically insignificant. In a meta-analysis of 7 prospective studies by Warkentin TE et al, patients developing HIT after UFH administration were predominantly females. (Odds ratio 9.22 vs 1.83, p value 0.02) They were unable to determine this effect in patients receiving LMWH due to paucity of HIT cases.[18]

UFH has been in use for more than a century now. Owing to its cost effectiveness, rapid onset of action, ease of reversal, inhibition of multiple coagulation factors and easy monitoring its likely to remain in use in future as well along with its derivatives, LMWHs.[20] Regular monitoring of platelet count and switching to newer anticoagulants in case of complications can maximize its benefits in VTE.

Conclusion

HIT is an established complication of heparin therapy. Use of LMWH significantly decreases chances of HIT as compared to UFH in patients presenting with DVT in medical wards.

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References

1. Despas N, Larock AS, Jacqmin H, Douxfils J, Chatelain B, Chatelain M, et al. Heparin monitoring: clinical outcome and practical approach. Ann Biol Clin. 2016;74(6):637-52.
2. Ashorobi D, Fernandez R. Thrombosis. [Internet] Updated: February 25, 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538430/#article-30111.s4
3. Generic Enoxaprin Questions and answers. [Internet] Updated: 02/06/2018. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm220037.htm
4. Menon H, Pillai A, Aussenberg-Rodriguez J, Ambrose J, Youssef I, Griffiths EA, et al. Cost reduction associated with heparin-induced thrombocytopenia panel ordering for enoxaparin versus heparin for prophylactic and therapeutic use: A retrospective analysis in a community hospital setting. Avicenna J Med. 2018; 8(4): 1338.
5. Provan D, Baglin T, Dokal I, de Vos J. Haemostasis and Thrombosis. Oxford Handbook of Clinical Haematology. 4th edition. United Kingdom: Oxford University Press; 2015. p454-545.
6. Leavitt AD, Minichiello T. Disorders of hemostasis, thrombosis & antithrombotic therapy. In: Papadakis MA, McPhee SJ eds. Current Medical Diagnosis & Treatment. McGraw Hill; 2018. p553-85.
7. Rivera OG, Corsi SO, Pavlovic JA, Aizman SA, Varas AP. Treatment of heparin-induced thrombocytopenia with rivaroxaban. Case report. Rev Med Chil. 2017;145(9):1213-7.[Spanish]
8. Choi JH, Luc JGY, Weber MP, Reddy HG, Maynes EJ, Deb AK, et al. Heparin-induced thrombocytopenia during extracorporeal life support: incidence, management and outcomes. Ann Cardiothorac Surg. 2019;8(1):19-31.
9. Salter BS, Weiner MW, Trinh MA, Heller J, Evans AS, Adams DH, et al. Heparin-Induced Thrombocytopenia: A Comprehensive Clinical Review. J Am Coll Cardiol. 2016;67(21):2519-32.
10. Schindewolf M, Steindl J, Beyer-Westendorf J, Schellong S, Dohmen PM, Brachmann J, et al.Use of Fondaparinux Off-Label or Approved Anticoagulants for Management of Heparin-Induced Thrombocytopenia. J Am Coll Cardiol. 2017;70(21):2636-48
11. Kang M, Alahmadi M, Sawh S, Kovacs MJ and Lazo-Langner A. Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity scorematched study. Blood. 2015;125:924-929.
12. Ramachandran P, Farag F, Morcus R, Gotlieb V. Autoimmune Heparin-Induced Thrombocytopenia: Treatment Obstacles and Challenging Length of Stay. Am J Case Rep. 2019;20:310-3.
13. Junqueira DR, Perini E, Penholati RR, Carvalho MG. Unfractionated heparin versus low molecular weight heparin for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2012;(9):CD007557.
14. Van Matre ET, Reynolds PM, MacLaren R, Mueller SW, Wright GC, Moss M, Burnham EL,et al. Evaluation of unfractionated heparin versus low-molecular-weight heparin and fondaparinux for pharmacologic venous thromboembolic prophylaxis in critically ill patients with cancer. J Thromb Haemost. 2018;16(12):2492-2500.
15. LindhoffLast E, Nakov R, Misselwitz F, Breddin HK, Bauersachs R. Incidence and clinical relevance of heparin induced antibodies in patients with deep vein thrombosis treated with unfractionated or low molecular weight heparin. Br J Haematol 2002;118(4):1137-42.
16. Lubenow N, Hinz P, Thomaschewski S, Lietz T, Vogler M, Ladwig A, et al. The severity of trauma determines the immune response to PF4/heparin and the frequency of heparin-induced thrombocytopenia. Blood 2010;115(9):1797-803.
17. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005;106(8):2710-5.
18. Warkentin TE, Sheppard J, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood 2006;108(9):2937-41.
19. Rothberg MB, Pekow PS, Lahti M, Lindenauer PK. Comparative effectiveness of low-molecular-weight heparin versus unfractionated heparin for thromboembolism prophylaxis for medical patients. J Hosp Med. 2012;7(6):457-63.
20. Arepally GM. Heparin-induced thrombocytopenia. Blood. 2017; 129(21): 286472.