

Original Article

FREQUENCY OF HEPARIN-INDUCED THROMBOCYTOPENIA 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 unfractionated 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 unfractionated (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 thrombocytopenia (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 thrombocytopenia. It occurs in ~5% patients receiving UFH and 0.5% of those receiving LMWH.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

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 patients 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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