Original Article

Incidence of thrombocytopenia one month after initiation of heparin during hemodialysis: An observational study

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ABSTRACT

Thrombocytopenia, a platelet count below 150 × 109/L, may be acquired or congenital. In patients with chronic kidney disease on hemodialysis, thrombocytopenia may be multi-factorial. However, the most worrisome of these is heparin-induced thrombocytopenia (HIT), as it causes thrombosis in various vital organs in addition to bleeding. Heparin is the mainstay of anticoagulation on hemodialysis to prevent clotting in the extra-corporeal circuit. HIT may be either Type 1 (non-immune) or Type 2 (immune). The protocol of testing for the presence of thrombocytopenia 1 month after starting heparin on hemodialysis is seldom followed and the exact incidence of HIT in eastern India is unknown. We studied hemodialysis patients in a tertiary care hospital in Kolkata over a period of 9 months. All of them had platelet counts checked after starting hemodialysis as per protocol. No patients had symptoms or signs of HIT. A drop in platelet count was noticed in 3 patients, but it was transient and attributable to other causes. It did not necessitate stopping of heparin and the platelet count spontaneously improved. So, it is reassuring that HIT is rare in the eastern part of India.

Key words: Contaminated heparin, Oversulfated chondroitin sulphate, Heparin-induced thrombocytopenia, End-stage renal disease, Anti heparin platelet factor 4 antibodies

Thrombocytopenia, or low platelet count, defined as a platelet count below 150 × 109/L, can be broadly classified as congenital and acquired. Acquired thrombocytopenia could be immune or non-immune [1]. Thrombocytopenia could be a result of decreased marrow production, increased destruction or sequestration/ consumption in the periphery, or a combination of decreased production and sequestration. Initial steps in the evaluation of thrombocytopenia include a review of the peripheral blood smear to exclude pseudo-thrombocytopenia due to platelet clumping [2].

The peripheral blood smear may also provide clues toward other causes of thrombocytopenia when combined with the complete blood count and a good patient history and physical examination. Platelet size and the presence of schistocytes, polychromasia, or spherocytes are some of the other features on the peripheral blood smear that help in diagnosing the etiology of thrombocytopenia [3].

Thrombocytopenia could be a serious medical condition such as thrombotic thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia (HIT). Therefore, it is always important for the treating physician to evaluate thrombocytopenia in a timely fashion so that the treatment for some of the serious conditions is not delayed [4]. The relevance of thrombocytopenia in the individual patient is variable and depends on the clinical presentation. Because platelets play an essential role in preserving vessel wall integrity [5].

Thrombocytopenia is associated with a defect of primary hemostasis. Clinically significant spontaneous

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bleeding does not usually occur until the platelet count is less than 10-20 109/L [6]. However, the presence of thrombocytopenia can aggravate surgical or traumatic bleeding or prevent the administration of effective treatment for several conditions (eg, antiviral therapy for chronic hepatitis C virus infection or cancer chemotherapy) [7].

In other situations, a low platelet count is the only initial manifestation of an underlying disorder that poses greater risks than thrombocytopenia itself (eg, HIV infection or myelodysplastic syndromes) or is an important marker of disease activity (eg, thrombotic microang-iopathies) [8]. Establishing the cause of thrombocytopenia has obvious clinical repercussions, but is sometimes quite challenging. This is particularly the case for hospitalized patients, in whom thrombocytopenia appears frequently in the background of a multisystem disorder and may be determined by multiple mechanisms [9].

Conversely, in the outpatient setting, thrombocytopenia is often isolated and asymptomatic, and the diagnosis of the specific cause is usually straightforward. Thrombocytopenia in pregnancy deserves special consideration because of the possible consequences on the fetus [10]. A structured approach to the diagnosis of thrombocytopenia involves the integration of clinical findings and appropriate support from the laboratory and other medical disciplines [11].

MATERIAL AND METHODS

The study was conducted in a prospective mode and was based on patients who were observed during the study period from 21st September 2020 to 4th May 2021. The study was carried out in the dialysis department of AMRI Group of Hospitals, Kolkata, Dhakuria. Formal permission for the study has been obtained from the respective IEC.

RESULT

Statistical analysis shows that in comparison of platelet count according to age and sex before and after heparin, 61-70 age group patients have more changes in platelet count than other age groups. Females have more changes in platelet count than males. No patients had symptoms or signs of HIT. Two patients dropped platelet count below 1L and one patient below 1.5L but did not. Develop thrombotic events. So heparin was continued. The thrombocytopenia was attributed to transient episodes of sepsis. The platelet count spontaneously improved again to >1L of two patients and one patient's platelet count improved again to >1.5L **(Table 1)**.

Table 1 – Patient details

Age	Sex	Platelet count before heparin	Platelet count after heparin
58	F	2.8	2.2
73	M	1.7	1.5
70	M	3.68	2
69	M	1.7	1.5
70	F	1.7	1.5
59	F	1.5	1.51
66	M	1.5	1.6
78	M	1.5	1.6
65	M	1.1	0.75
65	M	1.6	1.6
68	M	1.6	0.9
58	M	1.5	1.3
53	M	1.6	1.6
55	M	2.1	2.2
83	F	2.2	2
64	F	3.68	2
56	M	3	2
66	M	1.9	1.6
51	M	2.27	2.2

The pie chart **(Figure 1)** illustrates the platelet count before and after heparin according to age, whereas it reveals that the high platelet count before and after heparin is bigger at 61 to 70 age compared to other age groups.

According to **Figure 2**, which shows the platelet count before and after heparin according to sex, male patients have higher platelet counts both before and after heparin than female patients.

Figure 3 shows based on age and sex, it compares platelet counts before and after heparin, with the rate of platelet counts before heparin being higher than the rate of platelet counts after heparin. This shows that once heparin was started during hemodialysis, the amount of platelet count decreased.

Figure 4 shows the differences in platelet count before and after heparin based on age, clearly demonstrating that the platelet count before heparin is higher than the platelet count after heparin at various age groups. The changes in platelet count are also significant, with a 0.56 change from 61 to 70 years old.

The graph charts **(Figure 5)** illustrate how the platelet count has changed according to sex, with the platelet count before heparin being higher than the platelet count following heparin. Additionally, compared to men, women have greater variations in platelet count, which is 0.53.

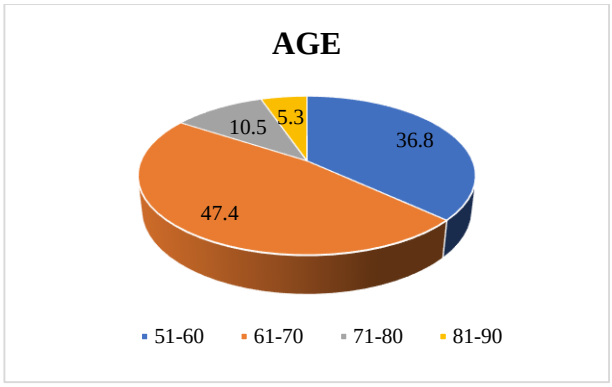

Figure 1 – Platelet count before and after heparin at different age groups.

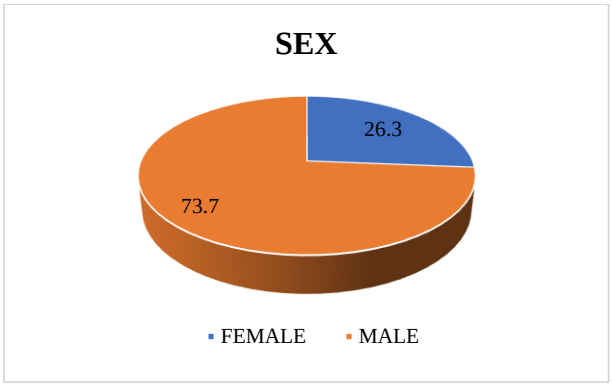

Figure 2 -Platelet count before and after initiation of heparin at different sex groups.

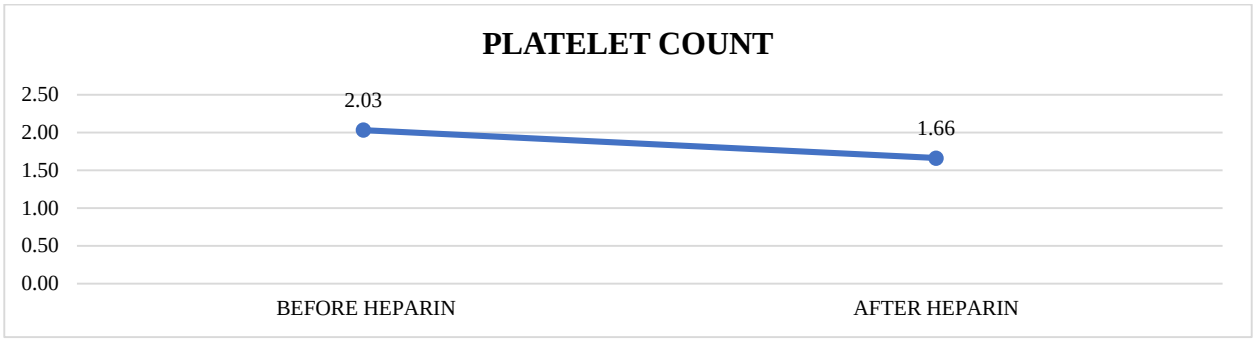

Figure 3 - Drop of platelet count before and after heparin based on age and sex.

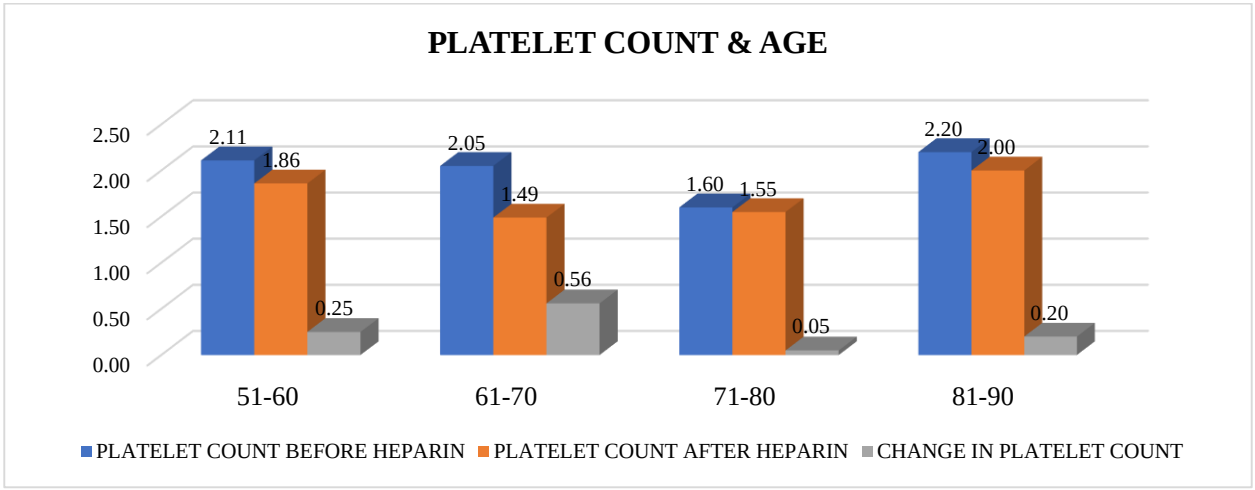

Figure 4 – Changes in platelet count before and after heparin based on age.

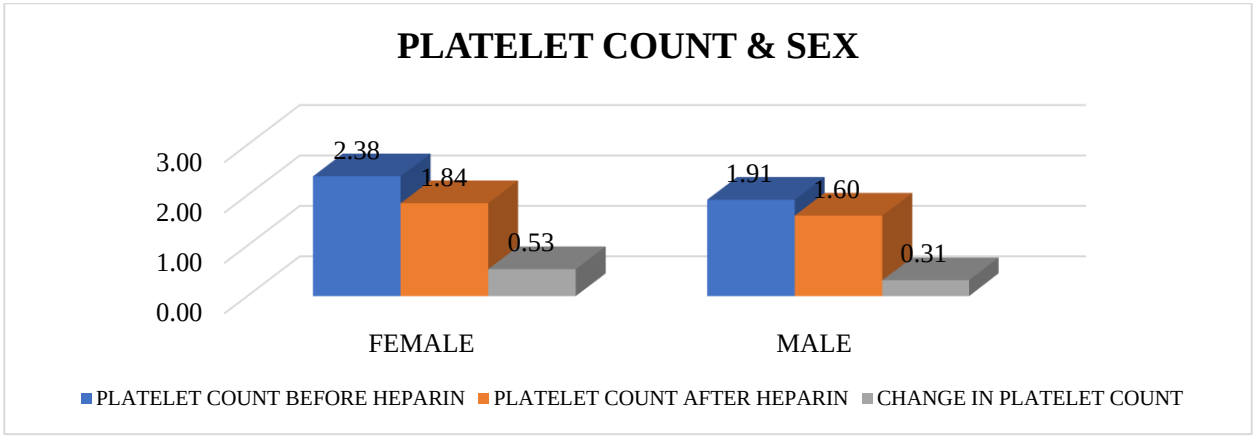

Figure 5 - Changes in platelet count before and after heparin based on sex.

DISCUSSION

Takfumi Matsuo et al. conducted a study on Heparin Induced Thrombocytopenia and Haemodialysis in dialysis patients with an unexpected fall in the platelet count, and/or unexplained thrombotic events, particularly visible clotting in the circuit under an adequate heparin dose, that begins between 5 and 10 days (between 7 and 30 days, mostly by the third to fifth session) after heparin initiation ELISA test result came positive, so in this case Alternative non-heparin anticoagulants like a direct thrombin inhibitor Argatroban was used as an alternative to heparin. Argatroban contributed to the rapid recovery of the platelet count and the disappearance of visible circuit clotting [12].

Robert E.Cronin et al., is conducted a study on Unfractionated Heparin for Haemodialysisin the 10,564 maintenance hemodialysis patients in the United Kingdom, the prevalence of HIT was 0.26per 100 patients and only 17% of these had complications related to the disorder. The disorder was typically discovered 5–10 days following exposure to unfractionated heparin and was characterized by a drop in platelet count and variable occurrence of a clotting event. Arterial disorders. The drop in platelet count was typically 30–50% below baseline and rarely reduced to the low levels seen with other drug-induced thrombocytopenias. When heparin was withdrawn, platelet counts typically recover to baseline within 2 weeks [13].

Jenny I. Shen, MD, MS and Wolfgang C. Winkelmayer et al. conducted a study on the Use and Safety of Unfractionated Heparin for Anticoagulation during Maintenance Hemodialysis in a 50-year-old man with a history of diabetes mellitus and end-stage renal disease (ESRD) became hypotensive 15 minutes into his dialysis session. He had been receiving maintenance hemodialysis through a left arteriovenous fistula 3 times a week for the past 5years without complication. He does not have a history of a bleeding disorder but takes 81 mg of aspirin daily. However, his abdominal pain worsened, so the hemodialysis treatment was discontinued and he was sent to the emergency department for further evaluation, later he had been transfused a total of 8 units of packed red blood cells. His hemoglobin level had stabilized at 9.5 g/dL. His platelet levels never decreased. The patient underwent anticoagulant-free hemodialysis acutely. After discharge, he was instructed to avoid taking aspirin [14].

C. WU et al., is conducted a study on Rivaroxaban for the treatment of suspected or confirmed heparin-induced thrombocytopenia studying Twenty-two consecutive adults with suspected or confirmed HIT received rivaroxaban 15 mg bid until a local HIT assay result was available. Participants with a positive local assay result continued rivaroxaban 15 mg bid until platelet recovery (or until day 21 if they had acute thrombosis at study entry), then stepped down to rivaroxaban 20 mg daily until day 30. The primary outcome measure, incidence of new symptomatic, objectively-confirmed venous and arterial thromboembolism at 30 days, occurred in one HIT-positive participant (4.5%; 95% confidence interval) and one HIT-positive participant required limb amputation despite platelet recovery. Platelet recovery was achieved in nine out of 10 HIT-positive patients with thrombocytopenia [15].

Timothy K. Liem, MD et al., conducted a study on Lepirudin as a safe and effective anticoagulant for patients with heparin-associated antiplatelet antibodiesinEighteen HAAb-positive patients received lepirudin. Lepirudin use was analyzed for indication, duration, and effectiveness of anticoagulation, and adverse events. HAAb presence was determined by platelet aggregation .9 had previous documentation of HAAb, 6 had thrombocytopenia while receiving heparin, and 3 had HAAb after a thrombotic event. The indications for lepirudin anticoagulation included thromboembolism prophylaxis arterial thrombosis pulmonary embolus or deep venous thrombosis and one each for atrial fibrillation, myocardial infarction, artificial heart valves, and hemodialysis access. The average duration of therapy was 4.04 days. Fifteen patients achieved adequate anticoagulation (activated partial thromboplastin time [aPTT] ratio > 2.0) with lepirudin. Seven patients had aPTTs that were sometimes supra therapeutic (aPTT> 100 seconds) but did not bleed. In all patients who had heparin-induced thrombocytopenia, platelet counts were normalized while they received lepirudin. There were two complications: one patient fell and had a calf hematoma (aPTT ratio 3.24) [16].

Joana Gameiro et al. conducted a study on Haemodialysis-related-heparin-induced thrombocytopenia Case series and Literature review in 5 patients between the ages 71 to 85 and had a history of hypertension, had chronic kidney disease, between this patient some had multiple myeloma and some had a bacterial infection, atrial fibrilization, and anemia. These 5 patients came with thrombocytopenia with low levels of platelet count in the hospital, warfarin and sodium citrate gave good results in platelet recovery and thrombocytopenia [17].

Makoto Harada et al. conducted a study on A Case of Heparin-Induced Thrombocytopenia That Developed in the Therapeutic Course of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis in an 87-year-old woman who presented with appetite loss and leg edema was

admitted for evaluation. Blood examination revealed an inflammatory response (C-reactive protein level was 7.85 mg/dL), kidney dysfunction (blood urea nitrogen was 37.4 mg/dL, and the serum creatinine level was 2.25 mg/dL), and hypoalbuminemia. Heparin calcium therapy was also administered. Reduction of 50% or more of the platelet count and a platelet decrease between 5 and 10 days after using heparin are consistent. Additionally, because the FDP-D-dimer was high, she might have had thrombosis. Heparin was discontinued 29 days after hospitalization, and argatroban therapy was administered. After starting argatroban therapy, her platelet count gradually increased. Fifty-two days after her hospitalization, the platelet count improved to 200,000/μL. However, because kidney function was not recovered, she was administered maintenance hemodialysis [18].

In this study, 19 patients experienced HIT after taking heparin recently (within 14 days). Through the analysis of sociodemographic data, it was found that the percentage of male patients (73.7%) was higher than the percentage of female patients (26.3%) (Figure 2). Male preponderance is seen in gender distribution in our study, which is similar to reports from other studies in countries of Asia. In India, less number of females may be due to higher illiteracy, social stigma, and the need for the male relative to be concerned and accompany the female for hospital visits. Maximum patients in this study were of age group 61-70 years (47.4 %) followed by 51-60years (36.8 %), 71-80 years (10.5 %), and 81- 90 years (5.3%) (Figure 1). A bimodal distribution is seen with the incidence of HIT. With a peak incidence in elderly patients and then in the first decade.

HIT has been recorded in individuals receiving hemodialysis while utilizing heparin anticoagulation, though heparin exposure for other purposes could not be ruled out. This study revealed 19 patients who experienced HIT after taking heparin recently (within 14 days) just to keep their blood vessels healthy while receiving renal replacement therapy. None of the patients showed an abrupt (within hours) development of HIT after heparin exposure, indicating a longer period possibly up to four months without prior heparin exposure. The immediate discontinuation of heparin and the initiation of alternative anticoagulation are recommended for treating patients with HIT. This approach decreases the 38–76% risk of thrombosis that persists for days to weeks (Figure 3).

Platelet counts typically recover more rapidly when patients receive alternative anticoagulant therapy, compared with historical control therapy. In the patients reported here, partial recovery of platelet counts occurred before argatroban discontinuation, the rate of new thrombosis was similar to that reported in previous studies of argatroban therapy in HIT, no one died of thromboembolic complications, and the bleeding risk was acceptably low (Figure 4, 5).

CONCLUSION

In 9-month research conducted in a Kolkata tertiary care hemodialysis facility, no incidences of HIT were found. A small number of patients developed thrombocytopenia without developing thrombotic events. So heparin kept going. The platelet counts spontaneously improved. As a result, we can conclude that HIT is probably fairly uncommon in the eastern part of India and the direct thrombin inhibitors lepirudin and bivalirudin, which are primarily cleared by renal and renal/enzymatic processes, respectively, have also been used for HIT therapy. However, argatroban, which is metabolized by the liver, is generally considered to be a better choice for patients with renal failure. The present findings emphasize the importance of heightened awareness of HIT in heparin-treated patients undergoing hemodialysis and of suspecting.

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