Study of Relationship Between Heparin and Platelets in Hemodialysis Patients.

Abstract

Platelets are considered one of the most important components of blood that contribute to the coagulation process, and they also play an important role in the blood clotting process. Platelets may be exposed to some types of anticoagulant drugs, such as heparin, which increases the risk of thrombocytopenia, especially in dialysis patients who receive heparin periodically in the extracorporeal circuit in the dialysis unit; thrombocytopenia may develop due to receiving heparin in every dialysis session, which has been confirmed for patients in previous research. This research, aims to find the relationship between heparin and platelets among dialysis patients.

Some parameters were carried on for hemodialysis patients of (Al-Jamil - Raqdalin - Zuwara) hemodialysis centers to support the study of the relationship between them, (CBC, PT, PTT, CT, and BT), also a questionnaire has been collected from the patients for further information.

The results showed that there is an inverse relationship between the dose of heparin and platelets at α (0.5), meaning that the higher the dose of heparin, the greater the thrombocytopenia. We also found that there is an inverse relationship between the duration of dialysis and platelets, meaning that the longer the duration of dialysis, the lower the platelet count. The results showed also the presence of clots in the dialysis machine in varying proportions.

We can conclude that there are no effects on the types of treatment doses on the platelets. Also, heparin dose and Platelets count have an inverse significant relationship. We can conclude also that there are no significant differences between the average platelets due to the types of heparin at the level of significance.

Keywords: *Heparin; Platelets Hemodialysis.*

1. Introduction

In general, heparin is used in hemodialysis units as an anticoagulant both in the extracorporeal circuit and in long-term hemodialysis catheters. Both unfractionated heparin and low atomic weight heparin can be used[1]. Heparin is the first choice when a rapid anticoagulant is needed because its effectiveness is immediate when not controlled by intravenous infusion. Heparin is controlled in low doses when used for primary prevention and in high doses when used therapeutically to prevent stroke recurrence [2]. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are the two most

widely used types of heparin [3]. UFH and LMWH don't have characteristic anticoagulant movement but potentiate the action of antithrombin III restraining actuated coagulation factors. These specialists comprise roundabout anticoagulants as their action is intervened by plasma cofactors[4]. We advise obtaining CBC, PT, APTT, and total body weight before beginning heparin medication. Regardless of the method, heparin effectiveness is dependent on dosage. When predicting effectiveness, the first dosage matters more than the APTT. A baseline platelet count is advised as a starting point from which to evaluate the potential development of Heparin Induced Thrombocytopenia (HIT)[5]. Thrombocytopenia is indicated by a blood platelet count of less than $150*10^9$/L(150,000/mm^3); however, spontaneous capillary bleeding typically does not occur until the count is less than $30*10^9$(30,000/mm^3)[6], the inception of this action starts with tissue injury and results in the delivery and restricting of a few glycoproteins, development factors, what's more, thickening elements. The intricacy of these cycles takes into account numerous pharmacologic targets, which gives a few choices with regards to antithrombotic treatment[7]. There are two types of heparin-induced thrombocytopenia (HIT) in hemodialysis patients: type I (HIT I), a mild, self-limiting condition that manifests 1-4 days after administration and accounts for 10%-20% of cases; The second type, known as HIT II, is severe; it begins between 5 and 15 days after the initial exposure to heparin and results in a decrease in the number of platelets that is greater than 30 to 50 percent lower than the baseline value.

The platelet count typically falls below 100 x 10/l[8]. Factually, thrombocytopenia following treatment with heparins, such as UFH and heparin derivatives like LMWH, is referred to as HIT. During HIT immune antibodies interceded by platelets assume a significant part, and cause a decrease in platelet count[9]. HIT happens when antibodies against multi-molecular buildings shaped by adversely charged heparin and the emphatically charged (platelets protein) platelet factor 4 (PF4) initiate platelets by means of the platelet FcyIIa receptor, prompting platelet micro-particle age and thrombin age[10]. In light of past information, we found that the PF4/heparin ELISA IgG test has a particularity of 93.5% and a responsiveness of 95.8%. In our ESRD populace, we have noticed a higher-than-expected number of patients that have middle of the road to high 4T score, a positive IgG PF4/heparin ELISA result

yet a negative SRA. The point of this examination is to assess 4T scores, PF4/heparin ELISA results, and SRA in patients with ESRD [11]. expanded clump development in extracorporeal circuit during hemodialysis with UFH is some of the time experienced by not just patients with HIT type II yet additionally those with HIT type I, this sort of HIT is credited to a direct ability of heparin to animate platelet aggregation, which prompts expanded platelet sequestration and resulting decline in platelet count[12]; in the concentrated consideration unite setting, continued coagulation of the extracorporeal circuit is the commonest appearance of HIT antibodies[13]. Antibodies against PF4/heparin are not an uncommon tracking down inpatients on persistent renal substitution treatment; HIT ought to be through when thrombocytopenia and additionally clump development happen during the initial 2-3 weeks after beginning of hemodialysis and during the initial fourteen days when patients on persistent dialysis[14]. it is necessary to avoid blindly giving symptomatic treatment such as platelet supplementation. This can easily lead to adverse events and increase the burden to patients. Clinician should aim at discovering the etiology in time, to avoid misdiagnosis and mistreatment. The authors in another study describe the presentation, diagnosis, treatment and outcomes of five cases of HD-HIT, and emphasize the importance of an accurate diagnosis and early intervention in order to reduce the mortality risk, which can be as high as 20%[15]. The study performed a retrospective review of patients with ESRD (creatinine clearance < 15 mL/min or on renal replacement therapy [RRT]) who underwent PF4 heparin ELISA testing from October 2015 to September 2019. True-positive PF4s required an intermediate to high 4T score (≥4), a positive SRA, and receipt of treatment for a HIT diagnosis. False-positive PF4s were defined as a positive PF4 with a negative SRA, low 4T score (< 4) or lack of treatment for HIT. Indeterminate cases were classified on the basis of clinical assessment by the treating team (eg, hematology or vascular medicine)[16]. Another retrospective study analyzed patients who were tested for evidence of positive anti-heparin antibody in the period from 2015 to 2020 in Zvezdara University Medical Centre. The diagnosis was confirmed by the 4T clinical scoring system, a positive antiheparin-PF4 ELISA test and a positive platelet aggregation test with heparin. the researchers stressed; HIT should be considered in patients at risk. It is necessary to abolish heparin treatment and use alternative

method (PD) or alternative anticoagulation. Hemodialysis patients have better prognosis than other comparable patients[17]. To determine the impact of CRRT on platelet count and development of thrombocytopenia, the researchers conducted a study: Retrospective analyses evaluated the intra-patient change in platelet count following CRRT initiation. Critically ill adult patients who received CRRT for at least 48 hours were included. The primary outcome was intra-patient change in platelet count from CRRT initiation through the first 5 days of therapy[18]. The heparin-platelet factor 4 antibody was positive and she was put on plasmapharesis. However, her condition further deteriorated and succumbed shortly. Heparin lock solution in the hemodialysis catheter was believed to be the cause of HIT in our patient[19]. Hence, HIT is a challenging diagnosis in ESRD patients, a population that has frequent exposure to anticoagulants, and a risk/benefit ratio should be weighed between the risk of progression to symptomatic HIT and the benefit of switching to a non-heparin anticoagulant bearing in mind the difficulties associated with the latter.

The diagnosis and treatment of HIT can be difficult in ESRD patients and requires careful consideration in order to provide appropriate care for this patient population. Alternative treatments are available, and clinical trials are ongoing to potentially prevent this condition from occurring in the first place. Therefore, a clinical approach should always be taken to address this issue[20].

2. Materials and Method

2.1 Patient sample

Ninety patients from dialysis centers in Al-Jamil, Raqdalin, and Zuwara, (59 males and 31 females), were targeted for this study through a letter from the dean of the college and obtaining the approval of the doctors supervising these centers, as well as the approval of the patients. In addition to the questionnaire, patients were informed that they would undergo tests to measure bleeding time and clotting time, and blood samples would be drawn from them to measure prothrombin time.

Coagulation tests

1. Bleeding Time and Clotting Time

Bleeding time and clotting time tests were performed directly on patients in dialysis units. The following tools were used: a glass slide, a stopwatch, cotton, filter paper, a scalpel, and 70% alcohol.

2. Prothrombin Time (PT)

The clotting time is measured at 37°C in the presence of tissular thromboplastin and calcium. It reflects the activity of Factor II (prothrombin), V (proaccelerin), VII (proconvertin), X (Stuart Factor) and fibrinogen. The measured time is converted into PT (%) or INR. Specimens of the test were: Blood/anticoagulant ratio: 4.5 mL of blood for 0.5 mL of sodium citrate 2 H2O 0.109 M. The coagulation analyzer used is Thrombostat.

2.2 Statistical analysis

All data collected from the questionnaire, from patient records, through examinations conducted directly on patients, or through collecting samples and conducting laboratory tests, was collected, transcribed, and statistically analyzed using Statistical Package for Social Sciences (SPSS) V24.

3. Results

The proportion of male patients who were investigated was 65.6% and the female was 34.4%. This percentage as presented in Table (1) below indicate that the percent of male is higher than female.

TABLE (1): *Displays the frequency and Percent for Gender*

Gender	Frequency	Percentage %
Male	59	65.6
Female	31	34.4
Total	90	100.0

While table (2) presented the percentage of the age groups, the percentage of the first age group 20-39 was 16.7%, the percentage of 40-59 years was the highest group with frequency 61.1%, and the age group of 60-79 was 22.2%.

TABLE (2): *Displays the frequency and Percent for Age*

Age (Years)	Frequency	Percentage %
20 – 39	15	16.7
40 – 59	55	61.1
60 – 79	20	22.2
Total	90	100.0

It is clear from Table (3) that the percentage of patients whose duration of dialysis is less than one year reached 14.4%, and the percentage of those whose duration of dialysis ranges from (1-6) years reached 57.8%, which represents the highest percentage, the percentage of those whose duration of dialysis ranged from (7-12) years reached 23.3% and the percentage of those whose duration of dialysis ranged from (13-18) years reached 4.4%.

TABLE (3): *the frequency and Percent for Duration of dialysis*

Duration (Years)	Frequency	Percentage %
Less than 1	13	14.4
1 – 6	52	57.8

7 – 12	21	23.3
13 – 18	4	4.4
Total	90	100.0

These data clarify that the percentage of patients taking UFH heparin are more than those taking LMWH, the percentage is 74.4% and 25.6% respectively. We also found that the percentage of patients who do not develop clots in the dialysis machine has reached 30%, while the percentage of patients in whom clots do not occur in all parts of the machine has reached 30%. The incidence of clotting in the "Line" stage was 5.6%. We note that the highest percentage of those who had clots during the (Filter, Line and Chamber) stage was 13.3%. The lowest percentage was in the "Catheter" stage, where it reached 1.1%, as shown in the table (4)

TABLE (4): *Displays the frequency and Percent for Clotting site in machine*

Clotting in machine Frequency Percentage%		
No	27	30.0
Line	5	5.6
Filter	2	2.2
Chamber	3	3.3
Catheter	1	1.1
Filter and Line	10	11.1
Filter, Line and Chamber	12	13.3
Line and Chamber	3	3.3
ALL	27	30..0
Total	90	100.0

It is clear from Table (5) followed that the percentage of patients in whom clotting occurred before or after the dialysis process reached 35.6%, while we find that the percentage of patients in whom clotting did not occur reached 64.4%.

TABLE (5): *Displays the frequency and Percent for Bleeding after and before dialysis*

Bleeding after and before dialysis	Frequency	Percentage %
No	58	64.4
Yes	32	35.6
Total	90	100.0

4. Discussion

This research indicates that the ages most at risk of developing chronic kidney failure are 40-59, which explains the development of chronic kidney disease at these ages or that the patient suffers from several diseases that lead to their exacerbation and entry into the dialysis stage. It is noted that the prevalence of dialysis is more common in men than women, as its rate in men is about 65.6%, while its rate in women is about 34.4%. We also found that the longest dialysis period was from 1 to 6 years, which indicates that the disease has spread significantly in the last 6 years,

and the proportion of patients receiving heparin will also increase as the number of patients receiving extracorporeal heparin increases. It was also confirmed in this research that there is no relationship between the different types of heparin used and the occurrence of thrombocytopenia in dialysis patients, which indicates that these two types differ in terms of bioavailability and half-life. We also found that there is no relationship between the occurrence of bleeding in the patient and its association with the occurrence of thrombocytopenia before and after dialysis because the dose of heparin does not cause bleeding due to the length of the dialysis session, which reduces the dose of heparin during the session. There is also no relationship between the occurrence of clots in the dialysis machine and the incidence of thrombocytopenia, and the largest percentage of clotting occurred in the parts of the machine, which are the filter, line, and chamber; when clotting occurs in these parts, the risk of clotting increases in the rest of the entire dialysis machine procedure. It has been confirmed that there is an inverse relationship between the dose of heparin and the number of platelets, meaning that the higher the dose, the lower the thrombocytopenia. Due to differences in the doses used the thrombocytopenia increases among patients. In this case there was also an inverse relationship between the duration of dialysis and platelets, that is, the longer the duration the fewer platelets, which accounts for the prevalence of thrombocytopenia in the long term in patients. The duration of dialysis increases the risk of thrombocytopenia in patients, which requires transferring the patient to alternative anticoagulants are less dangerous such as direct thrombin medications such as argatroban. In this research, we found that heparin flushes into the extracorporeal circuit causes clotting in the circuit, which increases the incidence of thrombocytopenia, which was discovered through a study conducted in Japan [21], this was confirmed in this study using a completely different analyzes such as ELISA assay, which was not used in our research despite the similarity of the results between the two studies, immediate ELISA is used after clinical suspicion of HIT, when HD-HIT patients show an elevated coagulation index or worsening of coagulation. In another study conducted at University Konya Turkey [22], says that patients are undergoing hemodialysis (HD) treatment have increased risk of developing HIT due to prolonged exposure to unfractionated heparin or low-molecular weight heparin. This study differed from ours in that

this study observed sever sepsis and thrombosis complicated by bleeding in the digestive system, which we did not notice in our research and did not address it. Confirming a study conducted in the USA [18], the use of heparin as CRRT is not necessarily associated with the presence of HIT; this is study differed from ours in that it showed a serial decreases in platelet count across multiple days after the start of CRRT, regardless of the dose of heparin given during dialysis. Previous research also differed from our research in that it relied on diagnosing thrombocytopenia using clinical T4 scores and PF4 antibodies , ELISA assay as evidence of the presence of HIT, as thrombocytopenia was diagnosed using these analyses by previous studies confirming the existence of a relationship between heparin and platelet; these studies were: ([11] , [15] , [16], [17], [19], [20] . However, in our research, these analyzes were not used as diagnostic tests, but rather tests were used to diagnose or monitor the dose of heparin that causes thrombocytopenia. Our research has been compared to similar research so that its results are identical or substantially similar to those mentioned above.

5. Conclusion

We can conclude from this study that there is an inverse significant relationship between heparin dose and Platelets count at (0.05). And we can conclude that there is an inverse significant relationship between the duration of dialysis and the Platelets count at (0.05). We also conclude that there are no significant differences between the average platelets due the types of heparin at the level of significance (0.05). Thus, we can say that there are no effects on the types of treatment doses on the platelets. Also we conclude that there are no significant differences between the average platelets due the bleeding during dialysis at the level of significance (0.05). Thus, we can say that there is no effect the bleeding during dialysis on the platelets.

6. References

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