Research Article

The Incidence of Heparin Induced Thrombocytopenia of Chronic Kidney Disease (CKD) Patients on Maintenance of Hemodialysis Visiting to HAH Hospital, Jamia Hamdard, New Delhi

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ABSTRACT

Aim: The present study was planned to record the incidences of heparin induced thrombocytopenia of Chronic Kidney Disease (CKD) patients on maintenance of hemodialysis. **Materials and Methods:** This is a prospective observational study, which enrolled 50 patients visiting dialysis unit after satisfying selection criteria. Different parameters like demographic details, educational status, working status, blood pressure, platelets counts, stage of CKD, etc. were recorded. The sources of data included physicians prescribing data, the patient's medication profile, questionnaire and laboratory test reports. The observations were recorded in the prescribed performs. **Results:** A total of 50 patients with CKD, 34(68%) were males, 16 (32%) were females, mean age 47.22 years with maximum number belong to age group 48-57 years. A total of 12% patients had a family history of CKD. About 26% of the total patients had a single concomitant whereas 24% of the patients had double concomitant conditions and the most frequent concomitant condition was anemia followed by hypertension. The Hb level was lower than the nomal limits and their eGFR level below 15ml/min/1.73m^2 hence they were all at stage 5 of CKD. All patients showed different platelet level and upon dialysis, it was decreased markedly. This showed that heparin induced thrombocytopenia during dialysis. Only 2 (4%) of the patient had clot formation in dialyzers and extracorporeal circuit and decrease in platelet count during hemodialysis. **Conclusion:** This study strongly recommends the monitoring of platelet count in CKD on maintenance of hemodialysis receiving heparin.

Key words: Heparin, Thrombocytopenia, Chronic Kidney Disease (CKD), Hemodialysis, Heparin induced thrombocytopenia.

INTRODUCTION

Chronic kidney disease (CKD) is defined by a reduction in the glomerular filtration rate (GFR) or urinary abnormalities or structural abnormalities of the renal tract. It is a common condition affecting up to 10% of the population in Western societies and is more common in some ethnic minority populations and in females.[1]

Thrombocytopenia is defined as a blood platelet count below 150*10^9/L (150,000/mm^3) but spontaneous capillary bleeding does not usually occur unless the count falls below 30*10^{9}L (30,000/mm^3). It may be due to a reduced rate of platelet production or increased rate of destruction.[2]

Heparin was utilized as an anticoagulant drug on a large scale, but now a days it is replaced by other newer anti-coagulant drug due to its adverse effects like bleeding, thrombocytopenia, alopecia, osteoporosis, hyperkalemia, elevation in hepatic transaminases and hypersensitivity reactions.[3-5] Nevertheless, it is a choice of drug in certain cases. Heparin comes under the indirect thrombin inhibitors group. This group includes unfractionated heparin, low molecular weight heparin (LMWHs) {enoxaparin, dalteparin, tinzaparin, nadroparin and raviparin} and fondaparinux and idraparinux. Heparin is strongest organic acid present in the body (in mast cell), yet not physiologically active anticoagulant.

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Commercially it is produced from ox lungs and pig intestine. It is not absorbed by the oral route, therefore, should be given either by subcutaneous or intravenous routes (intramuscular route is contra-indicated due to more chances of hematoma formation).[4,5]

LMWHs do not require the same intense monitoring as heparin thereby saving laboratory costs and nursing time. These advantages make LMWHs useful for both in-patient and outpatient drug therapy. Unfractionated heparin is metabolized by non-renal route so it is used effectively in renal failure. While, LMWHs and fondaparinux are excreted by kidney, therefore, contra-indicated in renal failure.[3,4]

Heparin-induced thrombocytopenia (HIT) is defined as a decrease in platelet count during or shortly following exposure to heparin.[6] Although it has been almost a century since the discovery of heparin, the features of HIT were first described in the early 1970s[7] followed by increasing reports of a condition suspected to have an underlying immunological basis. We now know that HIT is a potentially devastating immune mediated reaction caused by the development of IgG antibodies against the complex of heparin and platelet factor 4.[8] IgG/PF4/heparin complexes bind and activate circulating platelets through their Fc receptors promoting thrombin generation manifested by an increased propensity for arterial/venous thrombosis despite a falling platelet count. The condition often affects patient groups who are already at an increased thrombotic risk like in renal failure or requiring renal replacement therapy. Such patients often have coexistent causes for thrombocytopenia other than HIT.[6]

There are not enough data available regarding the use of unfractionated heparin and LMWHs used in CKD patients during the hemodialysis. Therefore, this observational study was planned to record the incidence of heparin-induced thrombocytopenia of CKD patients on maintenance of hemodialysis.

MATERIALS AND METHODS

This study was a prospective observational study in which 50 patients were enrolled based on inclusion and exclusion criteria and written informed consent was taken by them. These patients were visiting to the Dialysis Unit of HAH Centenary Hospital Jamia Hamdard, New Delhi-110062. The protocol was approved by Jamia Hamdard Institutional Ethics Committee (JHIEC) with reference no: JHIEC 12/12/ (19/16). All the results were presented as mean values.

Those patients who were receiving a heparin regimen with or without other medication and had age not less than 18 years were selected for the present study. At the baseline visit, patient's demographic data, medical history and family history were recorded along with previously available laboratory's investigation data and blood pressure. Follow-up patients were counseled and asked about any adverse drug reaction (ADR), their biological parameters and blood pressure were recorded. At the final visit, patients were counseled about any ADR and biological parameter were recorded and critically analyzed. Different parameters recorded were demographic details, pharmacotherapy details, blood and urine pathological reports, stage of CKD, blood pressure, educational status, working status, drug abuse etc. Efficacy markers like blood platelet count, blood hemoglobin level, eGFR levels were recorded.

All the data were collected directly from personal interviews of patients, physician prescribing data to the patients, medication profile and laboratory investigation reports of patients.

The study was conducted in compliance with current GCP, Ethical principles, Drugs and Cosmetic Act of Schedule Y for Clinical Trials regulatory requirements and followed the Basic Principles defined in ICMR ethical guidelines for biomedical research on human participants (2006) and CDSCO guidelines for Good Clinical Practices for Clinical Research in India.

The participants were informed before initiation of study through an oral presentation regarding the purpose, procedures to be carried out and rights of the subjects. The subjects understood and signed a consent form summarizing the discussion prior to admission for the study. The personal identity of the study participant was assigned by code number and was used in the record and results of the study. The name and address were not disclosed to anybody except the study personnel involved in the procedure.

RESULTS

The present study was carried out at the HAH Centenary Hospital associated with HIMSR, Jamia Hamdard, Hamdard Nagar, New Delhi-62. During the study period, a total of 50 patients on dialysis with Chronic Kidney Disease based on inclusion and exclusion criteria who visited dialysis unit of the HAH Centenary Hospital, HIMSR, Jamia Hamdard, New Delhi were enrolled in the study over a period of 4 months.

Among the total enrolled study population of 50 patients with chronic kidney disease, 34 (68%) were males and 16 (32%) were females, indicating that chronic kidney disease is more prevalent in the male gender.

The mean age of the patients included in the study was found to be 47.22 years. The maximum number of patients with chronic kidney disease fell under the age group of 48-57 years, followed by the age group of 38-47, 58-67, 28-37, 18-27, 68-77 years in male as well as in female subjects. The maximum no of male CKD patients belong to the age group of 48-57 years and female were also the highest in the age group of 48-57 years (Table 1). Table 2 described that 68% of the CKD patients were having a history of CKD since 0-1 years, followed by 20% since 2-3 years, 2% since 4-5 years, 4% since 6-7, 8-9 years and 10 or more years. The new cases were 68% (Table 2).

Our study recorded 50% of the patients were businessman followed by 22% house wives and the CKD patients were higher in pre-degree and graduate category and middle class people have more cases of CKD. As per Kuppuswamy's Socio Economic Status Scale and a total of 18% CKD patients were alcoholic and 8% smokers and 82% patients were non-vegetarian. The mean blood pressure of all the 50 patients was higher than the normal limits. The Hb level was lower than the acceptable limits (13.8-17.2 g/dL for males and 12.1-15.1 g/dL for females) and during the period of erythropoietin treatment, the percentage increased in the Hb level was 21.84% and 22.21% of the male and female respectively.

The platelet count varied, some showed a normal platelet count while others showed below the normal value. During the period of heparin treatment, the percentage decrease in the platelet level was found in male and female respectively (Table 3).

A total of 50% of patients had some concomitant disease. About 26% of the total patients had a single concomitant condition, whereas 24% of the patients had double concomitant conditions (Table 4). Thrombocytopenia was observed in two patients. The doses of heparin during hemodialysis in patients were 3ml as per normal body weight initial bolus infusion (Heparin Sodium IP 1000 IU). The decrease in platelet count more than 50% within fourteen to fifteen days indicated that heparin in those patients lead to thrombocytopenia (Table 4).

The most frequent concomitant chronic condition of the study population was found to be anemia 96% followed by hypertension 40%. Among patients with more than one concomitant condition the combination of anemia and hypertension was most common association (Table 5).

All the study population had their eGFR level below 15 ml/min/1.73m^2 hence they were all at stage 5 of CKD (Table 6).

The platelet level in some patients decreased markedly. This showed that heparin in these patients caused thrombocytopenia and 2 (4%) of the patient had clot formation in dialyzers and extracorporeal circuit (Table 7).

Table 1: Age distribution of CKD patients.

Age (years)	Male	Female	Total Patients	% of Patients (*n*=50)
18-27	5	2	7	14
28-37	4	1	5	10
38-47	6	4	10	20
48-57	9	7	16	32
58-67	7	2	9	18
68-77	3	0	3	6
Total	34	16	50	100

Table 2: History of CKD patients.

Years of CKD	Male	Female	Total	%(*n*=50)
0-1 year	24	10	34	68
2-3 years	7	3	10	20
4-5 years	0	1	1	2
6-7 years	1	1	2	4
8-9 years	1	1	2	4
≥10 years	1	0	1	2

Table 3: Blood pressure, haemoglobin level and mean platelet count with CKD patients.

Gender	Blood Pressure		Haemoglobin level		Platelet count		% decrease
	Systolic (mm Hg)	Diastolic (mm Hg)	Initial (g/dL)	Final (g/dL)	Initial (lakh/mm^3)	Final (lakh/mm^3)	
Male	141	72	8.197	9.988	1.73	1.63	6.01
Female	134	76	8.166	9.98	1.71	1.53	10.82

Table 4: Patients with concomitant diseases and patients developed thrombocytopenia. with CKD patients.

Concomitant disease	No. of patients	% of patients (n=50)	Gender	No of patients	Patients developed thrombocytopenia
Single concomitant disease	13	26	Male	34	2
Double concomitant diseases	12	24	Female	16	0
Total	25	50	Total	50	2

Table 5: Concomitant conditions with CKD patients.

Concomitant diseases	No. of patients	% of patients(*n*=50)
Anaemia	48	96
Hypertension	20	40
Diabetes	5	10
Hepatitis-C	5	10
Cardiovascular disease	1	2
Hypothyroidism	1	2
Depression	1	2
Arthritis	1	2

Table 6: Stage of CKD patients.

CKD stage	GFR Level (ml/min/1.73m^2)	Description	No of patients
Stage 1	≥90	Normal Kidney Function	Nil
Stage 2	60-89	Mildly Reduced kidney function	Nil
Stage 3	45-59	Moderately Reduced Kidney function	Nil
Stage 4	15-29	Severely Reduced Kidney Function	Nil
Stage 5	<15	Very severe or End stage kidney failure (sometimes called established renal failure)	All of the 50 patients

Table 7: Clinical profiles of the CKD patients studied.

Patient no	Age/sex	Diagnosis	Duration until onset after initiation of hemodialysis(days)	Platelets decrease (lakh/mm^3)	Clot formation during hemodialysis	Platelet aggregation induced by heparin
1	32/M	CRF due to high BP	15	1.4 to 0.78	+	+
2	25/M	CRF due to glomerulonephritis	14	2.2 to 0.73	+	+

Abbreviations: CRF, Chronic renal failure; + shows the presence

DISCUSSION

The focus of the present study was to evaluate the "heparin induced thrombocytopenia incidence in patients of chronic kidney disease (CKD) on maintenance of hemodialysis" attending the in-patient department (IPD) at HAH Centenary Hospital, a 350 bedded teaching hospital of Jamia Hamdard, associated HIMSR, New Delhi. In the present study it was reported that male patients were than female, indicating that chronic kidney disease (CKD) is prevalent in the male gender.[9] Similar observations were reported in other Indian studies[10,11] and one study in Nigeria[12] but different from a recent study carried out in Japan.[13]

The mean age of the patients included in the study was 47.22 years and CKD was more prevalent in the age group of 48-57 years. Males predominated in the study population, which was similar to that reported in other Indian studies.[9] Previous Indian studies reported mean age 38.69±15.5 years,[14] 47.4±14.9 years,[15] 42 ±13 years,[16] and 46.5±16.5 years.[11] The study patients in these studies were found to be younger as compared to one study population, which reported 56.6±12.2 years mean age.[17]

In the present study, 68% of the CKD patients had a history of CKD since 0-1 year, followed by 20% since 2-3 years, 4% since 6-7 and 8-9 years and 2% since 4-5 years and 10 or more years. The new cases were 68%. A total of 12% patients had a family history of CKD. Female patients (*n*=4, 8%) had more cases of family history than male (*n*=2, 4%). Similar results were reported in previous studies.[9] About 50% of the CKD patients in this study were businessman followed by 22% house wives.

There were 70% of the total patients belong to middle class people followed by 30% lower class among the total enrolled study population of 50 patients with CKD as per Kuppuswamy's socio-economic scale. It was also observed that CKD patients were higher in pre-degree and graduate category.

This study also reported that 82% patients were non-vegetarian, 18% alcoholic and smoker's similar results were reported in previous study.[9] Only 12% of CKD patients in our study were doing physical activity.

A total of 50% CKD patients had some concomitant disease. About 26% of the total patients had a single concomitant condition, whereas 24% of the patient had double concomitant conditions, which was similar to the findings of Oshawa, 2005.[18] In our study, anemia was the most common disease followed by hypertension, diabetes mellitus, coronary artery disease and infectious diseases. This was in agreement with previous studies.[19,20]The most frequent concomitant chronic condition of the study population was found to be anaemic (96%) followed by hypertension (40%). Among patients with more than one concomitant condition, the combination of anemic and hypertension was most common association. Similar results were reported in previous studies.[9,19,20]

The most common causes of chronic renal failure were hypertension, diabetes and glomerulonephritis, which was found to be similar as reported in previous Indian studies[10,14,21,22] and some foreign studies.[12,13,17,23-26]

Patients in the present study showed the hemoglobin level lower than the acceptable limits (13g/dL for males and 12g/dL for females) and their eGFR level below 15 ml/min/1.73m^2, hence they were stage 5 of CKD. The mean systolic blood pressure was found to be higher and the mean diastolic blood pressure it was lower from the normal limits. Our results are in agreement with the results reported in previous study.[9]

All the patients with CKD in the present study, heparin at a dose of 3ml in a normal body weight were administered. During hemodialysis and continuous renal replacement therapies require extracorporeal blood flow and to prevent clot formation in the dialyzer or occlusion in the extracorporeal circuits, same form of anticoagulant usually heparin was used.

During hemodialysis using heparin as the anticoagulant, two (4%) of the patients had decreased platelet count more than 50% within 15 days. Thus, we propose that heparin-induced thrombocytopenia (HIT) be considered as a diagnostic possibility when thrombocytopenia occurs in the patients of CKD on maintenance hemodialysis and receiving heparin for a long time. Our observations are similar to that reported earlier.[6,27]

CONCLUSION

HIT is a relatively uncommon but potentially fatal complication of the use of heparin in hemodialysis. It is associated with a risk of clot formation in the dialyzer and occlusion in the extracorporeal circuits. It may also lead to the risk of venous and arterial thrombosis due to the formation of a heparin platelet antibody. During hemodialysis of CKD patients, only 4% patients developed thrombocytopenia in the study period. The results of this study highlighted the need for comprehensive management of CKD patients. This study strongly recommends the monitoring of platelets count on regular basis.

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CONFLICT OF INTEREST

The authors declare no competing financial interest in publishing this research.

ABBREVIATIONS

CKD: Chronic kidney disease; **HIT:** Heparin induced thrombocytopenia; **GFR:** Glomerular filtration rate; **IPD:** In-patient department.

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