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HAEMOSTATIC DEFECTS IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Objective: To study Haemostatic defects in stage III and stage IV chronic kidney disease and to study coagulation marker in these patients.

Material and Methods: This study was conducted in the Nephrology and Haematalogy Department of Shaikh Zayed Hospital, Lahore from June 2010 to December 2010. The study included a total of 150 patients, 50 for stage III chronic kidney disease, 50 for stage IV chronic kidney disease and 50 for control group. Bleeding time prothrombin time, APTT, platelet count and D-Dimer were performed on these patients.

Results: A significantly elevated level of D-Dimer was found in 93% of the patients of stage III and stage IV chronic kidney disease. For stage III P. value .001 and for stage IV P. value .001 significantly elevated as compared to the control group less than 250ng /ml. Both PT and APTT for stage III and stage chronic kidney disease were within normal range. Bleeding time in stage III was within normal range, while in stage IV only 5 out of 50 patients had prolonged bleeding time. Which was significantly elevated as compared to control group (P. value <.002) platelet count in stage III, only 5 patients out of 50, had thrombocytopenia, while in stage IV only 9 out of 50 patient had low platelet count. Mean platelet count in stage III was 118.40 x $10^3/\mu l$ and in stage IV 115.44 x $10^3/\mu l$ thrombocytopenia seen in stage III and stage IV showed significant association with to disease of when compared with normal control group stage III P. value < .004 stage IV P <.005.

Conclusion: Chronic kidney disease both stage III and stage IV is assoated with coagulation abnormalities and bleeding disorder. So watch the patients closely with chronic kidney disease to avoid complication of bleeding tendency or thromboembolic phenomenon.

Key Words: CKD, D.Dimer, BT, PT, APTT, Thrombocytopenia.

INTRODUCTION

Chronic kidney disease (CKD) is a growing global health problem CKD is typically associated with a prothrombic tendency in the early stages of the disease where as in its more advanced stages that is end stage renal disease patients suffer from a prothrombic tendency and in many cases a bleeding diathesis.[1] Platelet dysfunction is observed mainly in advanced uraemia and is probably due to uraemic toxin present in circulation. Urea alone however is not responsible for platelet dysfunction and there is no correlation between blood urea nitrogen and bleeding time in chronic renal failure.[2] Other potential toxins include guadinosuccsinic acid and phenolic acid.

Thrombocytopenia, glomerular thrombosis and thrombi in small arteries and glomerular capillaries are common pathologic features in many renal diseases. Platelets are also involved directly in the pathogenesis of glomerular disease, through a variety of mechanisms including release of active molecules by enhancing immune complex deposition and by altering glomerular permeability.[3] Platelet dysfunction in CKD and ESRD also due to both intrinsic platelet abnormalities and impaired platelet vessel-wall interaction. The normal platelet response to vessel wall injury with platelet activation, recruitment, adhesion and aggregation is defective in advanced renal failure.[4]

Coagulation abnormalities associated with renal disease are seen in chronic renal failure, acute renal failure, nephritic syndrome, glomerulonephritis, neoplasm and renal transplantation. Abnormal platelet function occurs due to accumulation of toxic metabolites. hypercoagulopathy with predisposition to thrombosis can also occur, Fibrinolytic activity, anti-thrombin III and protein C are all reduced and factors V,VII,VIII and X are increased.[5]

Renal diseases may be also complicated by thromboembolic phenomenon. These are related to vascular access for dialysis. Upto 60% of patients with central venous catheter develop thrombosis.[6] Patients with chronic renal failure traditionally have been recognized as being at risk for perioperative bleeding and data suggest a hypercoagulable state in chronic renal failure.[7]

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Disturbances in haemostasis are common complications of kidney disease. Both bleeding diathesis and thromboembolism have been identified. The principle cause of these abnormalities is the uraemic state the pathogenesis of uraemic bleeding is multifactorial. The most important determinants of pathogenesis is increased levels of clotting factors, decreased levels of clotting inhibitors, diminished fibrinolytic activity and platelet hyperaggregability. At present the incidence of bleeding declining, where thrombotic complications have become the predominant cause of mortality.[12]

MATERIALS AND METHODS

This study was conducted in the departments of Nephrology and Haematology, Shaikh Zayed Hospital, Lahore from June 2010 to December 2010. Cases were divided into III groups. Group A included 50 cases for control group. Group B included 50 cases for stage-III CKD. Group C included for stage-IV CKD. Sample size calculated with expected difference in proportion of 0.17 (Specifically in CKDIV.99 and CKDIII.82) it is made a=.05 with two tailed test and power 83.7%. The required sample size is 50 per each group. Inclusion criteria was, all adult patients of chronic kidney disease of both ''genders with CKD III and CKD IV. Exclusion Criteria was, DIC, DVT, Septicemia & Patients on antiplatelet drugs.

Blood sample (5ml) was collected from chronic renal failure patients. 1.8ml was collected in a tube containing 200μl of 3.2% sodium citrate. The remaining blood was added to a tube containing EDTA to estimate erythrocyte sedimentation rate, haemoglobin, platelets and total leukocyte count. The citrated blood was centrifuged at 3000 rpm for 15 minutes. The separated plasma was used for prothombin time, activated partial thromboplastin time and D.dimer.

The haematological and coagulation investigations were performed on 100 cases of chronic renal failure coming to Shaikh Zayed Hospital, Lahore. Data were entered in special performa attached. D.dimer by latex agglutination method, bleeding time by Ivy's method, PT, APTT by manual method.

RESULTS

The present study included 100 cases of chronic kidney diseases, 50 for stage III and 50 for stage-IV. There were 25 males and 25 females in stage III and 30 males and 20 females in stage IV. In stage III CKD 7 out of 50 patients, D.dimer level was less than 250 ng/ml. 40 patients had value 250-500 ng/ml and 3 patients had value in the range of 500-1000 ng/ml.

Similarly in stage IV, 3patients out of 50 had D.dimer level in the range of 250-500 ng/ml. 42 patients had 500-1000ng/ml and 5 patients had D.dimer level between 1000-2000ng/ml. The mean value of two the groups were significantly elevated (P=.001) from normal value of control less than 250ng/ml.

The mean Prothrombin time (PT) in stage III was 12.64 $\pm$ 1.64 and stage IV was 12.50 $\pm$ .95 seconds respectively. There was no significance difference between the value of two groups and control group. In stage III only 2 patients out of 50 had prolonged APTT and stage IV only 5 patients had prolonged APTT than the control value mean APTT value of 2 patients in stage III was 35.50 $\pm$ 2.12 sec while 48 patients had value 29.47 $\pm$ 1.79 sec Mean APTT value of 5 patients of stage IV is 35.40 $\pm$ 2.60 sec and that of 45 patients is 29.47 $\pm$ 1.94. There was no significant difference of value between the two groups.

APTT is considered to prolonged if it is more than 7 second as compared to control group. The bleeding time in stage III was within normal range. Mean value was IV.71 $\pm$ 1.25 sec. While in stage IV only 5 out 50 patients had prolonged bleeding time with a mean value of 10.00 $\pm$ 1.22 sec while the rest of 45 had a mean bleeding time 5.18 $\pm$ 1.05 sec. There is no significance between the two groups but the prolonged bleeding time of 5 patients was significantly elevated from control value (P<.002). Regarding platelets counts in stage III, 45 patients (90%) had normal platelet count with a mean platelet count of 214.33$\pm$ 70.66 x$10^3/\mu$l only five patients (10%) had thrombocytopenia with a mean platelet count of 118.40 $\pm$ 24.90 x$10^3/\mu$l.

In stage IV thrombocytopenia was seen in 9 patients (18%) with a mean platelet count of 115.44$\pm$27.09 while the rest of 41 cases (82%) had normal platelet count with a mean value of 235.29$\pm$88.15x$10^3/\mu$l. Thrombocytopenia seen in both stages showed significant association with the disease of when compared with normal platelet count. The P value was <.004 for stage III and <.005 for stage IV. There is no significant different between the values of the two stages but low platelet count in stage III and stage IV has significantly lower than control group. Stage-III P<.004 and stage-IV P<.005.

DISCUSSION

In the present study coagulation profile, D.dimer level, PT, APTT, BT and platelet were studied. In the present study D.dimer levels were significantly raised in both groups. In total 100 cases 93 patients had significantly elevated D.dimer levels. A similar study has been carried on 49 patients of CKD, in which all the patients had showed significantly elevated levels of D.dimer.[14] An other 91 patients of CKD were studied in which all the patients showed elevated D.dimer levels[15].

Another study on 382 patients of CKD with hypertension had been conducted in which they all showed increased D.dimer levels significantly[16].

Disturbance of coagulation and fibrinolysis have been reported in patients with chronic kidney disease. Studies of different coagulation and fibrinolytic parameters have yielded conflicting results with some indicating suppressed fibrinolysis and other showing increased fibrinolysis. It is reasonable to assume that the higher level of D.dimer are primarily as a result of increased fibrin clot formation and breakdown. The increased thrombogenic state may be related to increased susceptibility to vascular disease in these patients[17]. In an other study had been performed in 18 diabetic nephropathy patients and 16 hypertensive patients with nephrosclerosis. Plasma level of D.dimer were significantly elevated[18].

The prothrombin time PT in stage III and stage IV were within normal control group. The APTT value in stage III showed only 2 patients had prolonged prothrombin time and stage IV only 5 patients had prolonged APTT. Prolonged APTT has also been reported in a study performed in 20 patients of diabetic nephropathy group[19]. Another study had been conducted to assess preoperatively coagulation profile in patients with chronic kidney disease no significant elevation was found in PT, APTT[9]. While in an other study PT was found shorter in diabetic nephropathy patients[20].

In the present study bleeding time in stage III was within normal range while in stage IV only 5 patients out of 50 had prolonged bleeding time. Renal failure was associated with severe haemorrhagic diathesis. A Study had been carried out to assess bleeding time in chronic kidney disease patients in which 33% patients prolonged bleeding time had been observed[21]. Patients with chronic renal failure frequently manifested a haemorrhagic diathesis characterized by prolonged bleeding time and intravenous estrogens have been shown to correct this abnormality[22]. In an other study several parameters of primary haemostasis and markers of activation of coagulation and fibrinolysis were measured in 48 patients with chronic renal failure, bleeding time was prolonged in 25/48 patients. Multivariate analysis showed that only platelet dysfunction and severity of renal disease were independent predictors of prolonged bleeding time in chronic kidney disease[23].

CKD is associated with prolonged bleeding time and impaired platelet function, which is further prolonged by the use of asprin[24]. In the present study, in stage III only 5/50 cases had thrombocytopenia, with a mean platelet count of 118.40 $\pm$ 24.90 and in stage IV, 9/50 had thrombocytopenia. Mean platelet count was 115.44 $\pm$ 27.09. A similar study was performed on 75 patients of chronic kidney disease out of which 11 had thrombocytopenia whose mean platelet was 118.3$\pm$25.05[25].

The frequency of thrombocytopenia in patients with chronic kidney disease is controversial. However, an other study was under taken to investigate platelet count in 55 patients with ESRD and 19 CKD. 31% patients had thrombocytopenia in haemodialysis group and platelet count in the other group is mildly reduced and thrombocytopenia is frequently present in CKD. A possible cause for platelet reduction is insufficient thrombopoietic activity[26]. But in another study diabetic patients associated with CKD had consistently raised markers of platelets activation[27].

CONCLUSION

All chronic kidney disease patients should be screened for coagulation defects to avoid bleeding trendency or any other thromboembolic phenomenon.

RECOMMENDATIONS

As the study recruited stage III and stage IV chronic kidney disease further studies are recommended in more advanced stage that is stage I, II & V, chronic kidney disease and also children suffering from kidney disease.

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