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Platelet Dysfunction in Uraemia: An Observational Controlled Experiment

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Abstract

Purpose: To study the platelet functions in patients with uraemia and compare them with control group of normal subject and to correlate platelet function with various parameters of renal function.

Methods: The subjects for the present study consisted of 50 patients with varying degrees of impairment of renal function due to diverse aetiology, and including a wide range of degree and duration of uraemia. Out of 50 cases studied, 20 were of Acute Renal Failure and 30 of chronic Renal Failure and 30 of chronic Renal Failure. 20 had evidence of bleeding at the time of study and 30 were without and evidence of bleeding. The etiological diagnosis was arrived at on the basis of appropriate investigation. The mean age in the cases of acute renal failure as 35.3 years. Out of a total of 50 patients 31 (62 per cent) were males and 19 (48 per cent) females. The duration was shortest in acute renal failure with a mean of 7.0 days S.D.±3.03 and range from 3 o 11 days whereas in chronic renal failure the mean was 568.54 days S.D. ±1189.3 and ranging from 3 to 5475 days.

Conclusion: The present study consists of fifty patients with varying degrees of impairment of renal function due to diverse aetiology, and an equal number of healthy subjects, age and sex matched. Of the 50 patients studied 20 were of acute renal failure and 30 of chronic renal failure. The results of this study demonstrate a rather high incidence of platelet dysfunction in uraemia.

Keywords: Bleeding, Clotting, Platelet, Renal Failure, Thrombocytopenia, Uraemia

Introduction

Uraemic bleeding is a well-recognized complication in patients with renal failure[1]. Almost 100 years ago in two patients with renal failure from Brights Disease who experienced severe and generalized bleeding[2].

Before the advent of dialysis, precise knowledge of clotting in terminally uraemic patients was of limited practical use since death was frequently imminent and unpreventable. Bleeding was also responsible for one-tenth of all deaths in acute renal failure. With the advent of modern procedures like dialysis and transplantation, the outlook is no longer hopeless and the avoidance and transplantation, the outlook is no longer hopeless and the avoidance and control of haemorrhage has assumed increased importance and control of haemorrhage has assumed increased importance[3]. The disturbance in haemostatic mechanism underlying such a tendency received little attention until the last two decades, a number of workers then attempted to define the nature of this defect and several possibilities were suggested. Lack of capillary integrity, thrombocytopenia, defect in plasma coagulation factors as well as qualitative platelet defect was put forward to explain the abnormal bleeding. It is now believed that the major coagulation defect of uraemic patients is a reversible qualitative platelet dysfunction[4]. Recent advances in management and prognosis of acute and chronic renal disease have made it desirable to undertake both clinical appreciation and a thorough laboratory investigation of incidence and nature of bleeding in renal failure[5].

With the advent of renal dialysis, the influence of biochemical alterations in uraemia on haemostatic mechanisms in general and platelets in particular have acquired an added significance. That a haemostatic defect exists in has been show several times. There is no general agreement regarding the nature of defect on the basis of available scientific studies.

Materials and Methods

The subjects for the present study consisted of 50 patients with varying degrees of impairment of renal function due to diverse aetiology, and including a wide range of degree and duration of uraemia.

These subjects were either admitted or referred to the nephrology unit of the department of Medicine, Hind Institute of Medical Science, Safedabad, Lucknow. These patients were investigated in the Hematology Laboratory of the Department of Pathology. Each patient was studies with control comparable to age and sex. This study was conducted in the department of medicine, Hind Institute of Medical Science, Safedabad, Lucknow. During 2007-2008.

All uremic patients who attended medicine/Nephrology OPD and were admitted in medicine wards were included in the study provided if they fulfilled the following inclusion and exclusion criteria.

Inclusion/ Exclusion criteria:

We have include the patients with criteria of patients with de-arranged renal profile, having no history of any known bleeding disorder, age more than or equal to 18 years, mentally and physically fit up to a minimum level required to participate in study. Exclusion criteria was patient less than 18 years, participants not interested/unable to provide informed consent, patients suffering from pre-existing liver disease, any substance abuse mental illness or medical condition that, in opinion of investigator would make it difficult for potential participant to participate in intervention, patients with known disorder of platelet dysfunction (Qualitative or Quantitative), patients receiving anticoagulant & ant platelet therapy.

Each case was evaluated through elaborate history, clinical examination and laboratory investigation with special emphasis to search for bleeding disorder.

Clinical assessment

Each patient was assessed according to the proforma prepared for the study. Besides noting down age, sex

and duration of illness, a careful history was obtained from each patient particularly in respect of any bleeding. An examination was then made including any evidence of bruising or active bleeding. Out of 50 cases studied, 20 were of Acute Renal Failure and 30 of chronic Renal Failure and 30 of chronic Renal Failure. 20 had evidence of bleeding at the time of study and 30 were without any evidence of bleeding. The etiological diagnosis was arrived at on the basis of appropriate investigation; following investigations were carried out in all subjects.

Evaluation of renal function was done by

Blood Urea, serum creatinine, serum potassium, serum calcium and serum phosphorus

Evaluation of platelet function was done by

Platelet count, bleeding time and clot retraction

Method

Each patient was studied with a control. Control and test samples were collected and tested in parallel employing the same technique. All blood samples were collected by venipuncture from the venous blood.

1. Blood Urea: Blood urea was done by DAM method.
2. Serum Creatinine: This was also estimated by alkaline picrate metnod.
3. Serum Electrolytes: Serum Sodium and potassium were estimated by ISE method.
4. Serum Calcium and Phosphorus: This was estimated by ISE method.
5. Serum Phosphorus: Phosphorus was estimated by the method described by King and Wootton, 1956.
6. Platelet Count: Platelet Counts were performed, using Rees Ecker fluid consists of sodium Citrate-3.8 gm, Brillant Cresyl Blue-50gm, Formalin-2ml and D. Water to make 100 ml.
7. Bleeding Time: It was estimated by Duke's Method.
8. Clot Retraction: Clot retraction was estimated according to the method of Macfarlane as described by Dacie.

Results and Discussion

The present study consists of fifty patients with varying degrees of impairment of renal function due to diverse aetiology, and an equal number of healthy subjects, age and sex matched. Of the 50 patients studied 20 were of acute renal failure and 30 of chronic renal failure. The results of this study demonstrate a rather high incidence of platelet dysfunction in uraemia.

The most simple yet a sensitivity measure of impaired platelet function is the bleeding time with venous stasis which was abnormal in 27 (54 percent) of the 50 cases with uraemia. It was also seen that 15 (75 percent) of the 20 bleeders had an abnormal bleeding time as compared to 12 (40 percent) of the 30 non-bleeders ($p < 0.05$). There have been divergent reports with regard to the abnormalities in bleeding time as reported by different authors and is due to lack of standardization and uniformity of techniques employed. There was abnormality of the Ivy bleeding time in the majority of their 26 patients with uraemia[8]. It was also found to be abnormal in all three cases of acute renal failure[9] and in 4 out of 5 cases of acute renal failure due to acute glomerulonephritis[10]. It was also seen that only 3 of their 21 other acute uraemics and 2 of 15 chronic uraemics showed prolongation of bleeding time. The bleeding time was prolonged in 2 of 12 patients with chronic uraemia and apparently in none of 30 chronic cases. In contrast, all patients with evident bleeding had a significantly prolonged bleeding time with venous stasis (Ivy bleeding time) but only 1 of the non-bleeders at the time of study had abnormal bleeding time[11]. It

was seen that significant thrombocytopenia was not a common feature in patients with renal failure being present in only 16 (32 percent) of the 50 patients.

It was further observed that only 4 (45 percent) of the 20 bleeders and 7 (23.33percent) of the 30 non-bleeders had thrombocytopenia (p>0.05).

Four patients (three patient of ARF and one patient of CRF) who was bleeding had a significant thrombocytopenia (platelet count <1,00,000 per cu.mm.). The patients with acute renal failure had found more thrombocytopenia as compare to chronic renal failure platelet. These finding related to the findings of Stewart who found thrombocytopenia to be more common in acute than in chronic uraemia of comparable severity. We found that thrombocytopenia was more common in bleeder (45 percent) than non bleeder (23.33) in contrast to thrombocytopenia occurred in uraemic patients; no significant difference existed between the platelet counts of those who did and did not bleed[8, 13]. While most authors agree that thrombocytopenia is not uncommonly seen in uraemia, the reported incidence of significant platelet depression (<150X10^3 per cu.mm) varies from 16 to 53 percent[14].

A series comprising 46 and 30 uraemic patients investigated the incidence of thrombocytopenia was 75 and 60 percent respectively[16]. In the largest reported series of 225 patients of uraemia studied to elucidate the nature of thrombocytopenia, the platelet life span was found to be normal in one fourth of all patients in acute renal failure and in one- twelfth of chronic renal failure cases who suffered from thrombocytopenia[6]. It is obvious that uremic bleeding is not correlated with platelet count and bleeding is frequently seen in the absence of significant thrombocytopenia. It is concluded that thrombocytopenia is not a important as qualitative platelet abnormalities, which are the most significant factors in the pathogenesis of uraemic bleeding. The lack of correlation between blood urea and platelet count (p=>0.05) and serum Creatinine and platelet count (p=>0.05) suggest that platelet counts are not affected in parallel with the rising blood urea and serum Creatinine values[9].

Poor clot retraction was seen in 8 (20 percent) of all 50 patients with renal failure. It was further observed that poor clot retraction was present in 6 (30 percent) of 20 bleeders and 2 (6.67 percent) of those without bleeding manifestation p<0.001. We found that most of patients with poor clot retraction also had markedly prolonged bleeding time (8 patients) and marked thrombocytopenia (7 patients)(≤1.1Lac per cu.mm).

Table 1: Age, Sex Distribution And Duration Of Illness

Groups	Age (Years)			Sex		Duration (Days)		
	Range	Mean	±S.D	Male	Female	Range	Mean	±S.D.
Acute Renal Failure	19-62	35.3	14.74	9	11	3-11	7	3.03
Chronic Renal Failure	35-80	51.47	11.62	22	8	3-5475	568.54	1189.3

Table 2: Occurrence of Bleeding Manifestation

Diagnosis	Total number of Patients	Patients with bleeding manifestation
Acute Renal Failure	20	12(60 Per cent)
Chronic renal failure	30	8 (26.66 per cent)

Table 3: The Occurrence of Bleeding Manifestation In Different Types Of Renal Disease

Diagnosis	Number of Cases	Number with bleeding manifestation
ACUTE RENAL FAILURE		
(a) Septic Abortion	6	5
(b) Multiple Fracture	3	3
© Septicemia	3	2
(d) PSGN	2	2
CHRONIC RENAL FAILURE		
(a) Chronic Pyelonephritis	12	4
(b) Bilateral Calculus Disease	3	2
© Chronic Glomerulonephritis	6	1
(d) Polycystic Kidney	3	1

Table – 4A: Assesment Of Renal Function

Tests	Controls			Renal Failure		
	Range	Mean	±SD	Range	Mean	±SD
Blood urea (mg %)	18-38	28.5	1.8	78-460	242.2	90.09
Serum Creatinine (mg %)	0.6-1.2	0.9	0.1	2.8-14.50	7.20	2.34
Sodium mEq/L	134-146	139.6	3.65	115-148	132.0	7.47
Potassium (m Eq/L)	3.0-5.0	3.98	0.48	4.0-6.3	5.28	0.54
Serum Calcium (mg %)	8.6-11.2	9.8	0.61	7.6-9.2	8.386	0.47
Serum Phosphorus (mg%)	2.2-5.0	3.1	0.5	3.4-7.0	5.21	0.89

Table:4B: Assesment Of Renal Function In Acute Renal Failure

Tests	Controls			Acute Renal Failure		
	Range	Mean	±SD	Range	Mean	±SD
Blood urea (mg %)	18-38	28.5	1.8	144-380	259.8	64.4
Serum Creatinine (mg %)	0.6-1.2	0.9	0.1	5.9.5	7.4	1.6
Sodium mEq/L	134-146	139.6	3.65	124-140	130.8	5.4
Potassium (m Eq/L)	3.0-5.0	4.0	0.5	4.4-6.2	5.3	0.4

Serum Calcium (mg %)	8.6-11.2	9.8	0.6	7.6-9	8.3	0.4
Serum Phosphorus (mg%)	2.2-5.0	3.1	0.5	3.4-6.4	5.1	0.8

Table: 4C: Assesment Of Renal Function Chronic Renal Failure

Tests	Controls			Renal Failure		
	Range	Mean	±SD	Range	Mean	±SD
Blood urea (mg %)	18-38	28.5	1.8	70.460	230.6	109.1
Serum Creatinine (mg %)	0.6-1.2	0.9	0.1	2.8-14.5	7.1	2.7
Sodium mEq/L	134-146	139.6	3.7	118-148	132.9	8.5
Potassium (m Eq/L)	3.0-5.0	4.0	0.5	4.6.3	5.3	0.6
Serum Calcium (mg %)	8.6-11.2	9.8	0.6	7.6-9	8.4	0.5
Serum Phosphorus (mg%)	2.2-5.0	3.1	0.5	4-6.8	5.3	1.0

Table: 5A: Assesment of Platelet Function

Tests	Controls			Renal Failure		
	Range	Mean	±SD	Range	Mean	±SD
Bleeding Time	1.5-7.0	3.73	1.44	2-12.5	7.05	3.12
Platelet count x lac per Cu.mm.	1.90-4.20	3.07	70.57	0.82-4.10	2.21	0.98
Cloth Retraction (Percent)	62-86	73.06	6.21	48-78	67.12	8.58

Table: 5B: Assesment Of Platelet Function Acute Renal Failure

Tests	Controls			Renal Failure		
	Range	Mean	±SD	Range	Mean	±SD
Bleeding Time	1.5-7.0	3.73	1.44	2-12.5	7.05	3.12
Platelet count x lac per Cu.mm.	1.90-4.20	3.07	70.57	0.82-4.10	2.21	0.98
Cloth Retraction (Percent)	62-86	73.06	6.21	48-78	67.12	8.58

Table 5C: Assesment Of Platelet Function Chronic Renal Failure

Tests	Controls			Renal Failure		
	Range	Mean	±SD	Range	Mean	±SD
Bleeding Time	1.5-7.0	3.73	1.44	2-12.5	7.05	3.12
Platelet count x lac per Cu.mm.	1.90-4.20	3.07	70.57	0.82-4.10	2.21	0.98
Cloth Retraction (Percent)	62-86	73.06	6.21	48-78	67.12	8.58

Table 6: Bleeding Time

Bleeding time (Minites)	Number of Cases	Percentage
<7.0	23	46
7.0-9.0	12	24
9.1-11.0	10	20
>11.0	5	10

Table 7: Platelet Count

Platelet count lac/cu.mm.	Number of Cases	Percentage
-1.00	8	16
1.01-2.00	14	28
2.01-3.00	14	34
3.01-4.00	10	20
4.01-	1	2

Table 8: Clot Retraction

Clot Retraction (per cent)	Number of Cases	Percent
-50	4	8
51-60	6	12
61-70	22	44
71-80	18	36

Table – 9: Frequency of Abnormalities In Platelet Counts, Bleeding Time And Retraction In Acute And Chronic Renal Failure

Diagnosis	Thrombocytopenia	Prolonged bleeding Time	Poor clot Retraction
Acute Renal Failure (20)	10	14	5
Chronic Renal Failure (30)	6	13	3

Table 10A: Assesment of Renal Function In Bleeders And Non-Bleeders In Uneamia (Arf& Crf)

Tests	Patients with Bleeding Manifestations (20)			Patients without Bleeding Manifestations (30)		
	Range	Mean	±S.D	Range	Mean	±S.D.
Blood Urea (mg%)	204-408	288.7	64.0	78-460	213.8	99.0
Serum Creatinine (mg%)	5.3-14.50	8;50	2.0	2.8-11	6.4	2.2
Sodium (mEq/L	115-145	128.5	7.5	116-148	134.2	6.7
Potassium (mEq/L)	5.1-6.30	5.5	0.3	4-6.2	5.2	0.6
Serum Calcium (mg%)	7.6-9	8.3	0.4	7.6-9.2	8.5	0.5
Serum Phosphorus (mg%)	3.4-7	5.5	0.9	4-6.8	5.0	2.6

Table 10B: Assesment of Renal Function in Bleeders and Non-Bleeders In ARF

Tests	Patients with Bleeding Manifestations (20)			Patients without Bleeding Manifestations (30)		
	Range	Mean	±S.D.	Range	Mean	±S.D.
Blood Urea (mg%)	208-380	283.3	56.7	144-350	224.5	61.8
Serum Creatinine (mg%)	6.1-9.5	7.8	1.3	5-9.2	6.7	1.9
Sodium (mEq/L	124-135	129.9	6.2	126-140	132.1	4.2

Potassium (mEq/L)	5.1-6.20	5.5	0.3	4.4-5.8	5.1	0.5
Serum Calcium (mg%)	7.8-9	8.3	0.4	7.6-9	8.5	0.5
Serum Phosphorus (mg%)	4.4-6.2	5.2	0.8	3.4-6.4	4.9	0.7

Table 10C: Assesment Of Renal Function In Bleeders And Non-Bleeders In CRF

Tests	Patients with Bleeding Manifestations (20)			Patients without Bleeding Manifestations (30)		
	Range	Mean	±S.D.	Range	Mean	±S.D.
Blood Urea (mg%)	70-460	207.0	115.5	200-380	295.8	68.5
Serum Creatinine (mg%)	2.8-11	6.3	2.4	6.4-14.5	9.3	2.5
Sodium (mEq/L	123-148	134.6	7.3	118-145	128.0	8.3
Potassium (mEq/L)	4-6.2	5.2	0.7	5-6.3	5.5	0.4
Serum Calcium (mg%)	7.6-9	8.5	0.5	7.8-9	8.3	0.5
Serum Phosphorus (mg%)	4-6.8	5.1	0.9	4.6-6.4	5.9	0.9

Result

Blood urea: The Blood urea in patients with renal failure had a mean of 242.28 mg/100ml. S>D>±94.09 with a range from 78 to 460mg/100ml.

Serum creatinine: The mean value of patients of renal failure was 7.2mg/100ml, S.D.±2.34 with a range from 2.8 to 14.50mg/100ml

Serum sodium: The mean value of patients of renal failure was 132.04 mEq/Litre, S.D.±8.84 with a range from 115 to147 meq/litre.

Serum potassium: The mean value in uraemic was 5.28mEq/litre, S.D. ±0.54 with a range from 4.0-6.3 mEq/litre. It was seen that a higher (greater than normal plus 2 SD) value of potassium was obtained in 40 cases (80%).

Serum calcium: The mean calcium in patients with renal failure had a mean of 8.386 mg/100ml. S.D.±0.47 with a range from 7.6-9.2mg/100ml. It was seen that a lower (normal mean minus 2 SD) value of serum calcium was found in 29 patients of the 50 cases.

Serum phosphorus: The mean value in uraemic was 5.21 mg/100ml. S.D.±.89 with a range from 3.4 to 7.0 mg/100 ml. it was seen that a higher (greater than normal plus 2 purpura SD) value of phosphorus was obtained in 46 cases.

There was statistically significant correlation between blood urea and bleeding time, serum creatinine and bleeding time, serum calcium and bleeding time and serum phosphorus and bleeding time. The P value for bleeding time <0.05, platelet Count >0.05, Clot retraction >0.05 respectively

Conclusions

Uremic bleeding is a well-recognized complication in patients with renal failure. Before advent of dialysis, precise knowledge of clotting in terminally uremic patients was of limited practical use since death was frequently imminent and unpreventable. Bleeding was also responsible for one-tenth of all deaths in acute renal failure. With the advent of modern procedures like dialysis and transplantation, the outlook is no longer hopeless and the avoidance and control of haemorrhage has assumed increased importance. Lack of capillary integrity, thrombocytopenia, defect in plasma coagulation factors as well as qualitative platelet defect was put forward to explain the abnormal bleeding. It is now believed that the major coagulation

defect of uremic patients is reversible qualitative platelet dysfunction. Recent advances in management and prognosis of acute and chronic renal disease have made it desirable to undertake both clinical appreciation and a thorough laboratory investigation of the incidence and nature of bleeding in renal failure.

Ethics approval and consent to participate

Consent for participation was must.

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