Prolonged Bleeding Time in Uraemia

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Key wards: 1-Deamino-S-D-Arginine vasopressin, bleeding time, haemodialysis, peritoneal dialysis, serum creatinine, packed cell volume, partial thromboplastin time, plate let, von Willebrand factor, calcium ion, chronic renal failure, gastrointestinal tract, genitourinary tract, prothrombin time, white blood cell count, blood **urea.**

Summery:

Bleeding is a common and sometime fatal event in uraemic patients. Its etiology is multifactorial.Eighty uremic patients were included in this study. 39 were males and 41 were females. Their ages ranged 18-70 years. They received haemodialysis (HD), peritoneal dialysis (PD) or both. Bleeding time (BT) was measured by intravenous method. BT is considered prolonged if it is > 10 minutes.This study found neither the patients' age nor their sex affect the BT. The effect of duration of the illness on BT is remarkable. HD affects BT while no effect for PD was found.The commonest clinical manifestation of uraemic bleeding tendency is epistaxis.Among the variable characters of uraemic patients that adversely affect BT were raised serum creatinine (S. cr.), low packed cell volume (PCV), and prolonged partial thromboplastin time (PTT).This study recommends measurement of BT as a simple bedside test for uraemic patients to identify the risk of bleeding at early time. Corrections of abnormal variables like:Anemia by eryhtropoiten and/or blood transfusion,azotemia by dialysis,3-DDAVP usage and/or cryoprecipitate for acute bleeding episode,and estrogen therapy and others.Have a good impact on treating bleeding in uraemics.

الخلاصة

يعتبر النزف حدث شائع و أحيانا مميت لدى مرضى بولينية الدم وهو متعدد الأسباب . لقد تضمنت هذه الدراسة ثمانين مريضا مصابا ببولينية الدم ، تسع و ثلاثون منهم ذكورا و واحد و أربعون إناثا. لقد تراوحت أعمار المرضى بين ثمانية عشر إلى سبعين سنة. لقد عولج المرضى بالديال الدموي ، الديال الصفاقي أو بكلاهما معا.اعتبر زمن النزيف طويلا إذا كان اكثر من عشر دقائق بطريقة داخل الوريد. لم يؤثر كلا من عمر أو جنس المرضى على زمن النزيف ، بينما كان لمدة المرض الأثر الواضح عليه. إن ديال الدم كان مؤثرا على زمن النزيف و لم يكن للديال الصفاقي اثر يذكر.اكثر المضاهر السريرية لنزعة النزف لدى مرضى بولينية الدم شيوعا هو الرعاف. إن أهم المتغيرات المؤثرة سلبيا على زمن النزيف لدى مرضى بولينية الدم هي : ارتفاع نسبة مصل لحمينين الدم ،هبوط النسبة المؤوية الحجمية لكريات الدم الحمراء و إطالة زمن الثرمبوبلاستين الجزئي.لقد زكت هذه الدراسة زمن النزيف كفحص جانب سريري بسيط لتحديد خطر النزف لدى مرضى بولينية الدم. إن لتصحيح المتغيرات غير الطبيعية الدفع الجيد في علاج النزيف لدى مرضى بولينية الدم و تشمل هذه المغيرات ما يلي:تصحيح فقر الدم بإعطاء معزز تكون الكريات الحمراء أو بنقل الدم،تصحيح تنترج الدم بالديلزة، استعمال علاج(DDAVP) 1-Deamino-S-D-Arginine vasopressin أو الراسب البارد لنوبات النزيف الحادة و المعالجة بالا ستروجين أو غيره.

Introduction.

Bleeding is a common and sometimes fatal event in uraemic patients. Although the etiology of hemorrhage in those patients is multifactorial, the major cause is plate let (PL) dysfunction and impaired interaction between PL and vessel walls. A direct

correlation exists between prolongation of BT and clinical bleeding in uraemic patients. However pathogenesis of uraemic PL defect is not entirely clear. Many abnormalities have been described including:

Impaired PL adhesion,reduced thromboxan A^2 synthesis that is possibly due to defective cyclo-oxygenase action,abnormal binding of von Wille Brand factor (vWF) to PL or subendothelial surfaces,storage pool defect, and decreased PL aggregation in response to exogenous agonists.Whether these abnormalities reflect the presence of plasma-born inhibition or abnormality of PL function is unknown. An abnormality in the concentration of cytoplasmic calcium Ca^{+2} in resting or stimulated PL could explain most of the manifestation of uraemic PL defect,this is because of many PL function require cytoplasmic or extrinsic Ca^{+2}[(1)]

In 1764, Giavanni Battista Morgagni[(1)] described a patient with uremia in whom the main clinical feature was bleeding from the stomach and nose. In 1827 Richard Bright emphasized that patients with renal failure often presented with purpura[(1)]. After dialysis was introduced, hemorrhage became less common among renal failure patients, and with improvements in the management of uremia. The bleeding generally consists of ecchymosis, purpura, epistaxis, gum bleeding and only rarely manifests as severe hemorrhage. However, bleeding can still be fatal complication of uraemic patients needing major surgery or invasive procedure e.g. kidney or liver biopsy[(2)]. Uraemic bleeding has long been known to have multifactorial origin:

1.Acetyl salicylic acid has been prescribed for patients who undergoing haemodialysis to reduce thrombosis of the vascular access and to improve dialysis efficiency. Thus 160 mg of acetyl salicylic acid effectively prevented shunt thrombosis, in chronic renal failure (CRF). Acetyl salicylic acid induces prolongation of BT in uraemic more than in normal people.

2.Anemia: BT and PL adhesion are influenced not by PL number only, but also by red cell number, hence the anemia of renal failure has been regarded an important factor associated with prolonged BT and probably plays a major role in the pathogenesis of uraemic bleeding tendency. The current management of uraemic bleeding includes adequate dialysis, red cell transfusion or eryhtropoiten to patients with severe anemia and acute bleeding episodes may be treated with DDAVP which in most patients is rapidly effective, at least on BT. Patients undergoing major surgery and with recent gastrointestinal or intracranial bleeding need longer lasting control of haemostasis and seem to be the most likely condition for conjugated estrogen therapy [(3)]. Recently, recombinant human erythropoiten has been shown to shorten the BT with a parallel rise in PCV level to 30%. Clinician should be aware that a diminished PCV might contribute to the bleeding tendency already present in patients with thrombocytopenia.

3.The possibility that an abnormal vWF in uremia accounts for the prolonged BT and reduced PL adhesions has been intensively investigated but are not confirmed.

4-PL-PL interaction: several abnormalities of PL-PL interaction have been found. Reduced ex-vivo PL aggregation in response to various stimuli has been reported with some inconsistency between the various findings.

5-Parathyroid hormone: finding of increased PLs cyclic Adenosine monophosphate and PL Ca^{+2} content in uremia drew attention to the possible role of parathyroid hormone in uraemic PL dysfunction. PTH has already been proposed as uraemic toxins because of its suspected role in most of the clinical features of uremia such as anemia,peripheral neuropathy and osteoarthropathy. This is due to PTH inhibits PLs aggregation in- vivo and induces accumulation of adenosine monophosphate and calcium in various tissues.

6.Thromboxan A2 and prostacycline: uraemic PLs generates less thromboxan A2 than normal PLs and uraemic patients have an increased vascular prostacycline (PGI2) formation.
7.Defects in PL adhesion and aggregates formation in uraemic bleeding disorders that can be attributed to inhibitory factors in plasma PL adhesion to the subendothelial region of blood vessels. In the formation of haemostatic plugs, PL adhesion is followed by a stimulus, which induces PL aggregation .In addition to a PL adhesion defect, decreased aggregate formation was also found in uraemic perfusates[4]. Normal PL in uraemic patient showed similar results, which indicates that a factor in uraemic plasma accused this adhesion and aggregation defect.

The aim of this study is to estimate the prevalence of bleeding tendency in uremia. The clinical presentation of uraemic bleeding was assessed.

Methodology:

In this study, 80 patients were enrolled. Their ages ranged between 18-70 years. Thirty-nine of them were males and 41 were females. The study was conducted over a period of 13 months starting from August 2000. All the patients were suffering from uremia and were treated with HD, PD or with both. They were collected from Medial City Teaching Hospital and Alnehrane Teaching Hospital .BT was measured at the bed side by the method of mielke et al [5] with a simple (general diagnosis) template to make a fife mm horizontal incision on the volar surface of the forearm. BT more than or equal to ten minutes was considered prolonged (normal BT up to 9 minutes)
This study evaluates the effects of various variables of uraemic patients on their bleeding tendency. These variables were prothrombin time (PT), PTT, PL count, white blood cell count (WBC), PCV, blood urea (BU), and S. cr. The primary cause of CRF and its effect(s) on BT was evaluated. This study also concentrates on the effects of the type and the program of dialysis on BT.

Statistical analysis that were used in this study were Chi square and Z-test of unpaired samples, P value < 0.05 was considered significant

Results.
The age of the patients with CRF has no significant effect on the prolongation of BTas in figure 3-1.
***0.5>P>0.25**

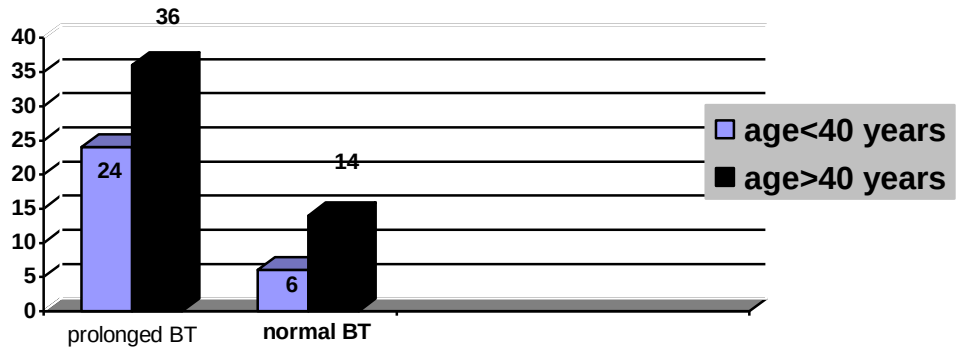


Figure 3-1:the effect of age of the uremic patients on BT.

This study also evaluates the effects of various variables of uraemic patients on their bleeding tendency.The prevalence of prolonged as equal among both sexes,see figure3-2.
***P>0.9 by Z test.**

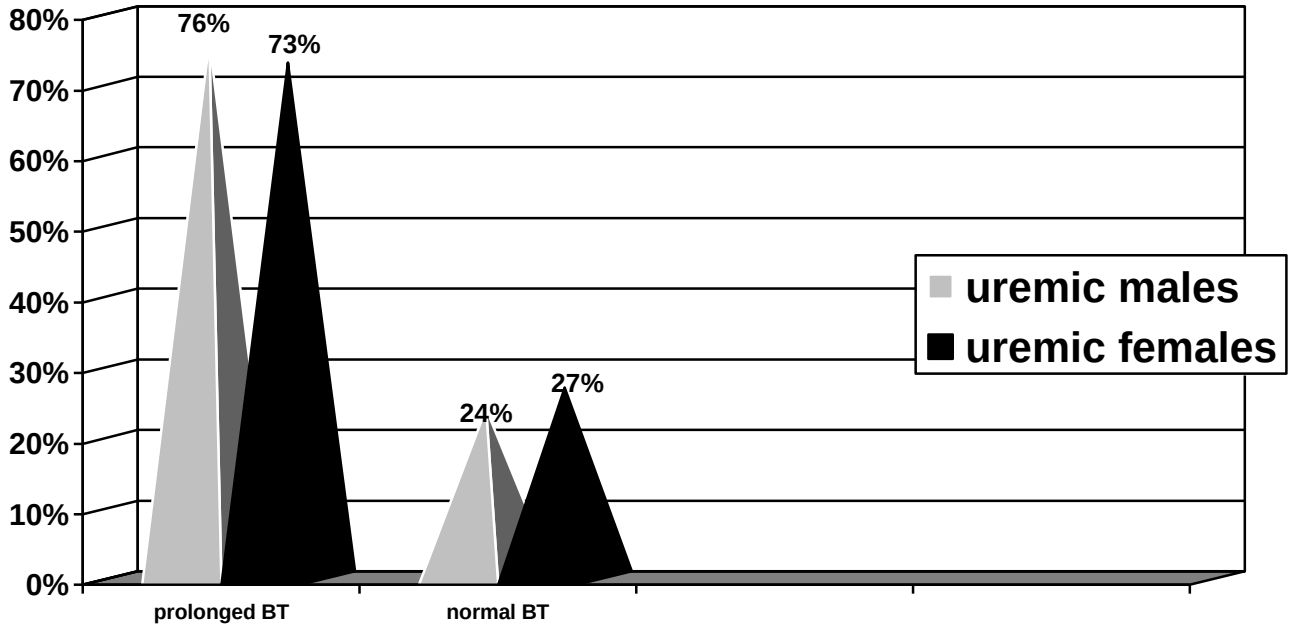
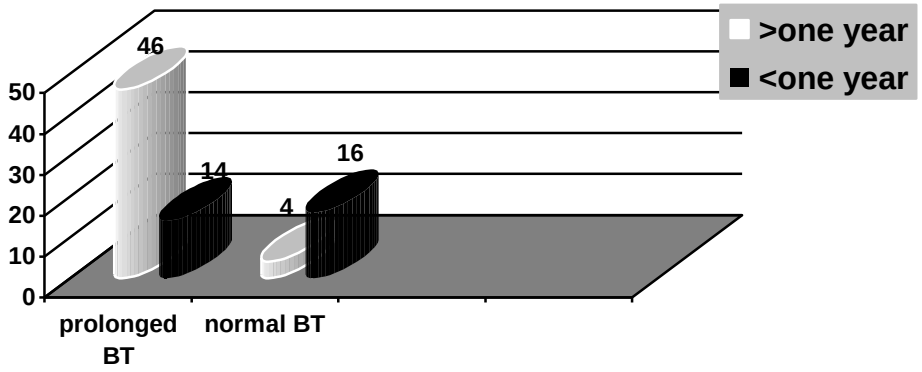
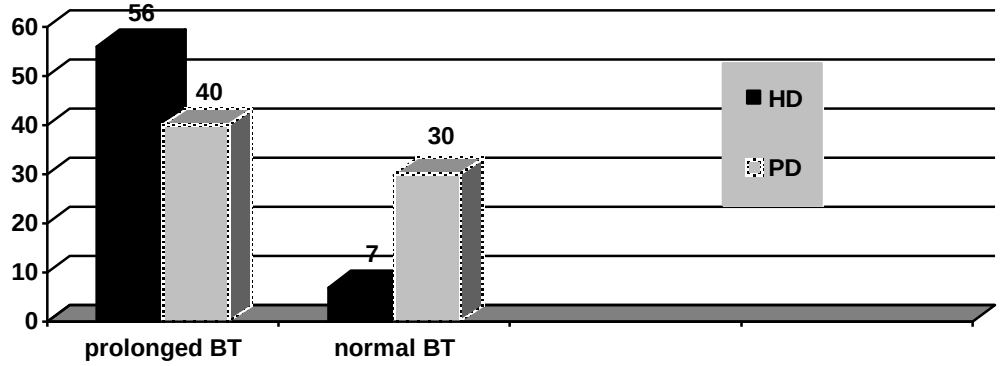


Figure 3-2: shows no effect for the sex on the BT in uremia.
The duration of CRF has a highly significant effect on the prolongation of BT,Fig. 3-3.



P<0.001(highly significant).
Figure 3-3: shows the effect of duration of uraemia on BT.

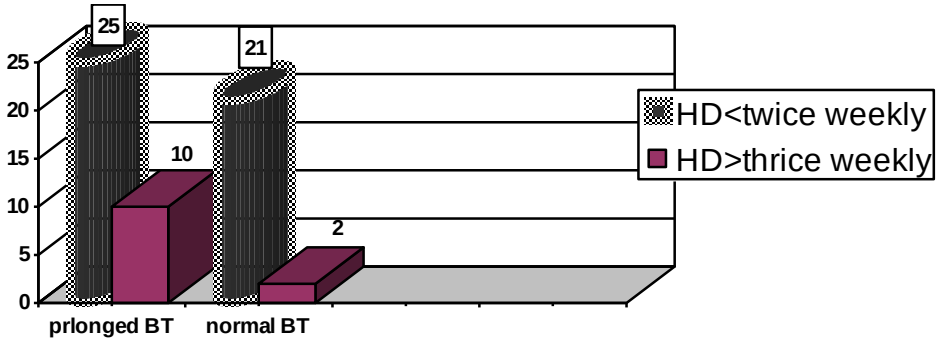
BT and consequently bleeding tendency was more common among patients who were treated by HD in comparison to those treated by PD (Fig. 3-4).



***0.05>p>0.25**

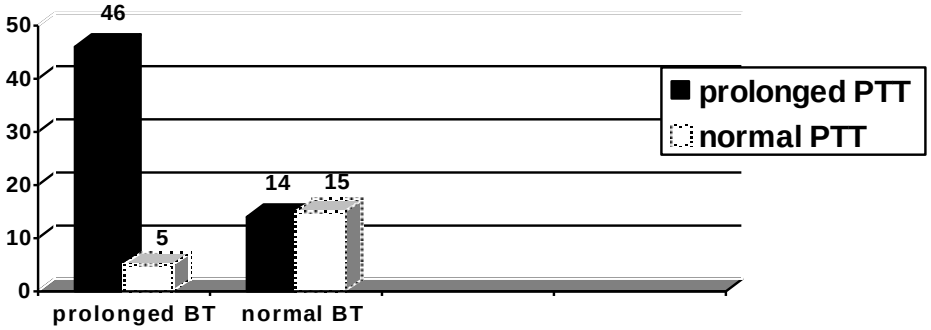
Figure 3-4:the effect of the method of dialysis on BT in uraemics.

While the program of PD has no effect on BT (Fig. 3-5), frequent HD programs (thrice weekly) has a significant effect on the BT prolongation.



***0.025>P>0.01,**Four patients with unknown program of HD and 18 patients did not undergo HD were excluded.**

Figure3-5: the program of haemodialysis has a significant effect on BT prolongation.

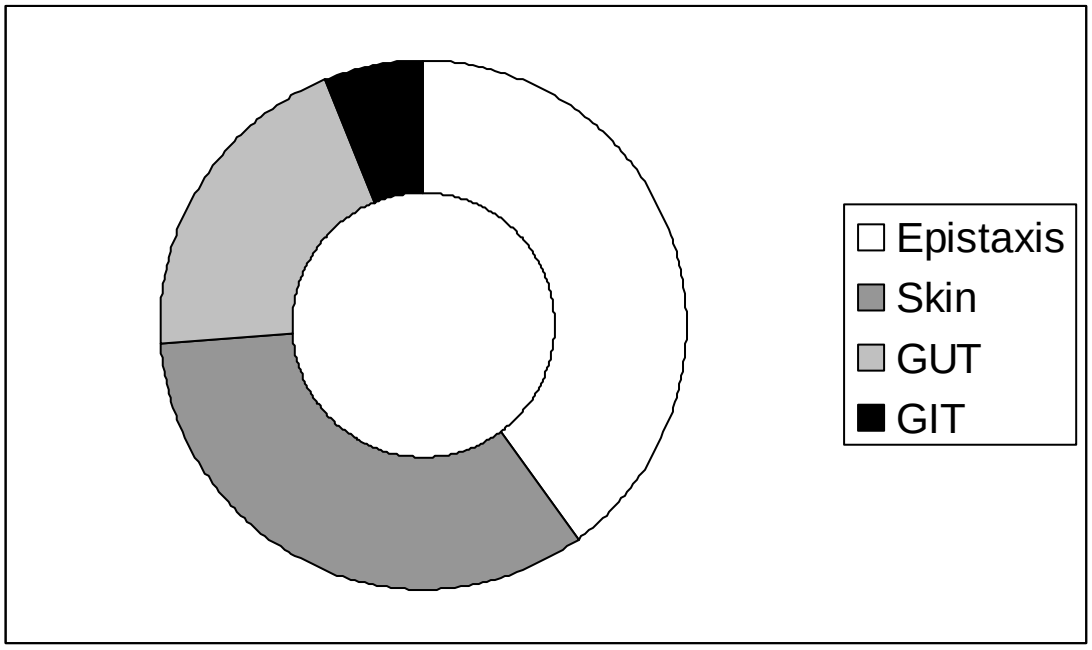


***0.1>P>0.05**

****Eight patients with unknown number of PD were excluded from this study.**

Figure 3-6:the program of PD has no significant effect on BT.

The most common clinical presentation of uraemic bleeding was epistaxis 40%. Cutaneous 34% especially in those undergone PD.Gastrointestinal tract bleeding (GIT) 20% come next in the list. Genitourinary bleeding (GUT) was rare 6%. Cerebral, intraperitoneal, pericardial and intraocular bleeding were not seen in our patients, see figure 3-7.



Fiure 3-7: clinical presentation of uraemic bleeding.
***0.05>P>0.025.**

Figure 3-8:shows significant association between prolonged BT and prolonged PTT

We found a significant association between prolonged BT and prolonged PTT (Fig. 3-8), while there was no significant association between prolonged BT and prolongation of PT see figure 3-9.

***0.5>P>0.25.**

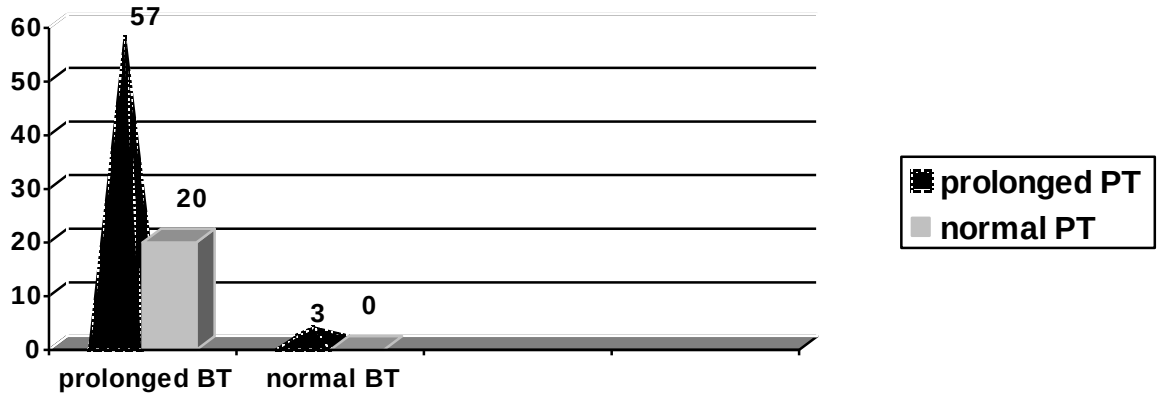


Figure 3-9: the relation between BT and PT.

The most common cause of CRF in our study was diabetes mellitus. The highest incidence of bleeding was among patients with primary renal disease due to systemic hypertension, obstructive uropathy and renal secondary amyloidosis (Tab. 3-1).

Table 3-1: the incidence of prolonged BT of uraemics in relation to the primary cause of uremia.

Cause of uremia	Prolonged BT	Normal BT	total	%
Urinary tract infection	10	5	15	66%
Diabetes mellitus	14	3	17	82%
Systemic hypertenson	14	0	14	100%
Obstructive uropathy	3	0	3	100%
Nephrolithiasis	2	4	6	33%
Nephrotoxic drugs	4	2	6	66%
Systemic lupus erythematosus	2	2	4	50%
Familial Mediterranean fever +amyloidosis	1	0	1	100%
Polysystic kidney	0	1	1	0.0%
Unknown	8	5	13	62%

We found a higher incidence of bleeding in patients treated with calcium channel blockers alone or in combination with diuretics. Also more common in diabetics treated with oral hypoglycemic agents as compared to insulin (Tab. 3 -2).

Table 3-2:The effects of medications on BT in uremia.

Medication	Prolonged BT	Normal BT
Nifedipine	14	0
Furosemide	60	20
Nifedipine+furosemide	14	0
NSAID	17	7
Antibiotics	60	20
Oral hypoglycemic agent	6	1
Insulin	4	2

Among variables of uraemic patients that adversely influence the BT was low PCV <30% and higher S.cr. >6 mg/dl. There was no effect of other variables on BT (Tab. 3-3).

Table 3-3: the effects of variables of uraemics on the incidence of bleeding tendency and BT prolongation.

Variables	Prolonged BT	Normal BT	Total
PL count*			
≤175000/ml	12	3	15
>17500/ml	0	65	65
PCV***			
<30%	49	2	51
≥30%	11	18	29
WBC count*			
≤4000/ ml	20	2	22
>4000/ml	40	18	58
BU*			
≥100MG%	31	18	49
<100MG%	29	2	31
S.cr.**			
≤6mg%	15	17	32
>6mg%	45	3	48

*P>0.05

**0.05>P>0.025

***0.01>P>0.025

Discussion:

In this study we found no effect of patient's age on BT. This is probably attributed to the shorter life span of both extreme age groups, since there is no enough time to have vascular structural changes to develop. The technical limits of renal replacement therapy are behind the shorter life span of children and elderly patients with CRF. That's why Mezzano D et al[7] had positively correlated the prolonged BT with age of patients. There was no importance of the patient's sex in the prolongation of BT, which may be due to our small sample size; However, we observe a relatively higher incidence of BT prolongation among males. This may be attributed to the low level of estrogen in males.The importance of the prevalence of bleeding in uraemic males had led to the use of recombinant estrogen (premarin) in the long-term management of uraemic bleeding complication. This is consistent with Couch P and Stump Shemin D et al [8] and Heunisch C et al [9].

The longer the duration of CRF, the more the effect on prolongation of BT. The enough time for vascular changes to develop may explain this observation. Richardson and Lordon [10] found that bleeding from GIT to be a significant source of blood loss in some patients with CRF treated with chronic HD. Gheissan A et al [11] noted a higher prevalence of angiodysplasia of the upper and lower GIT in CRF patient. Walkowiak et al[12] found that a specific antigen sequence of protein containing degradation products in uraemic plasma is correlated with progression in renal failure.The cause of significantly higher incidence of bleeding tendency in uraemics receiving HD compared to those receiving PD is multifactorial: The usage of heparin in HD,the HD introduces a tendency to (thrombophilia), [13] acquired factor VIII inhibitors. [14] and the quality of HD filters and its synthesized material may play a role in PL dysfunction in CRF. [15-16]

Other studies concluded that while dialysis frequently effective for the short term, it does not completely correct PL dysfunction [17-18]. Butt et a1 [14] disagreed with their study and as us he showed that both PD and HD resulted in significant improvement in prolonged BT because of the usage of regional heparinization or low molecular weight heparin. In our study, we found a significant association between the prolonged BT and prolonged PTT while no relation between BT and PT. This is due to:

Most of our patients with prolonged PTT were receiving HD treatment,uraemia induces acquisition of factor VIII inhibitor [16] ,ineffective binding of the vWF to PL membranes,and acquired PL storage pool deficiency [8] .

Reissell et al[19] found that increased PT in both diabetic and non-diabetic uraemics compared to the controls.We noted that the commonest presentation of bleeding tendency in our patients according to frequency were epistaxis, cutaneous, GIT and GUS. The skin bleeding is probably due to surgical trauma during the procedure of PD. Remazz G et al [20] showed that cutaneous hemorrahgic manifestations are usually mild, i.e. ecchymosis or purpura but can be severe in occasional patients who may have GIT or intracranial bleeding. We did not encountered intracranial, intraocular or pericardial bleeding in our patients. The frequent HD program and abundance of pericardiocentesis may explain the absence of pericardial bleeding in our results. Richardson et al [10] resulted in an attribution of the GIT bleeding in uraemic to small angioplastic lesion. Similarly Gheissari et al found angiodysplasia in both upper and lower GIT as a culprit for GIT bleeding. [10] Chen et al [21] reported acute esophageal ulcer, which causes massive bleeding on HD as a rare cause of GIT bleeding. He suggested that inflammatory mucosal changes of upper GIT including stomach and duodenum are well documented in uraemic patients and assumed to be the major source of upper GIT bleeding. GUT bleeding may have a casual relationship with uraemic bleeding. Most of

our patients with GUT bleeding have a local cause in addition to prolonged BT. Couch and Stumpf et al [3] found the most common manifestation of uraemic bleeding are epistaxis, purpura and GIT bleeding. Therefor, we advise endoscopic study for uraemics with GIT bleeding and further controlled studies are required.

We found higher incidence of uraemic bleeding in hypertensive patients, those with obstructive uropathy and renal amyloidosis. The inability to increase vascular resistance in response to elevation in pressure might promote over perfusion of the more distal vasculature leading to hemorrhage formation. Since uraemia promotes bleeding tendency, such alterations along with vascular myogenic function could initiate or aggravate hemorrhage formation.Salazus [23] found that patients with CRF with bleeding tendency exhibited increased local level of prostacycline (PGI2) a potent PL inhibitory eicosanoid in response to injury. In contrary to our study, Rissell et al[10] found diabetic uraemic patients have a slightly prolonged BT like that in non-diabetic group, however, we advocate a further standardized controlled study to identify the relationship between the primary renal disease and bleeding tendency. We observed a higher incidence of uraemic bleeding among hypertensive patients receiving calcium channel blockers, this is consistent with J. Antony et al [1] who concluded that the PL defect seen in some patients with uraemia is associated with a decreased rise in PL (Ca^{+2}) after stimulation and that this is a manifestation of an intrinsic PL defect. For unknown reason we found higher incidence of bleeding in diabetic uraemic receiving oral hypoglycemic drugs.

There was significant effect of anemia on BT. It is theorized that an increase in circulating red cells increases PL radial movement and interaction with endothelium. Recently recombinant human eythropoiten has been shown to shorten the BT with a parallel rise in PCV level to 30%[4]. Tong et al[24] proved that erythropoiten increases the number of circulating PL and improves PL function. [25]

Our study found no effect for PL count on BT. This is agreed by Gawas et al [26] who postulated that bedside defect of PL, a dense granular content is demonstrated in PL of uraemic patients. Anad A and Feffer[4] found that BT is prolonged in uraemic patients independent of their PL count and is shortened by elevating the PCV. On the contrary, Michalak et al [27] resulted in that the smaller PL circulating mass in uraemics may contribute to bleeding diathesis in uraemia and disturbed thrombocytopoeisis occurs in CRF.

Our study showed no relationship between the level of B.U and BT. Since dietary protein intake, drugs, state of hydration and GIT bleeding affect BU, its level has no significant relation to severity of CRF. This is in consistent with Jaiyesimi et al [18] who found a significant correlation between BU and BT prolongation. The absence of the mentioned factors in his patients, the smaller sample in his study may explain the difference. The higher the S.cr.level above 6mg/dl, the more common the BT prolongation. The later is consistent with Mezzano et al, Krawczyk et al [28] and Moosa et al [5]

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