THE EFFECT OF D.D.A.V.P ON PLATELETS IN CHRONIC UREMIC PATIENTS WITH BLEEDING

Thesis

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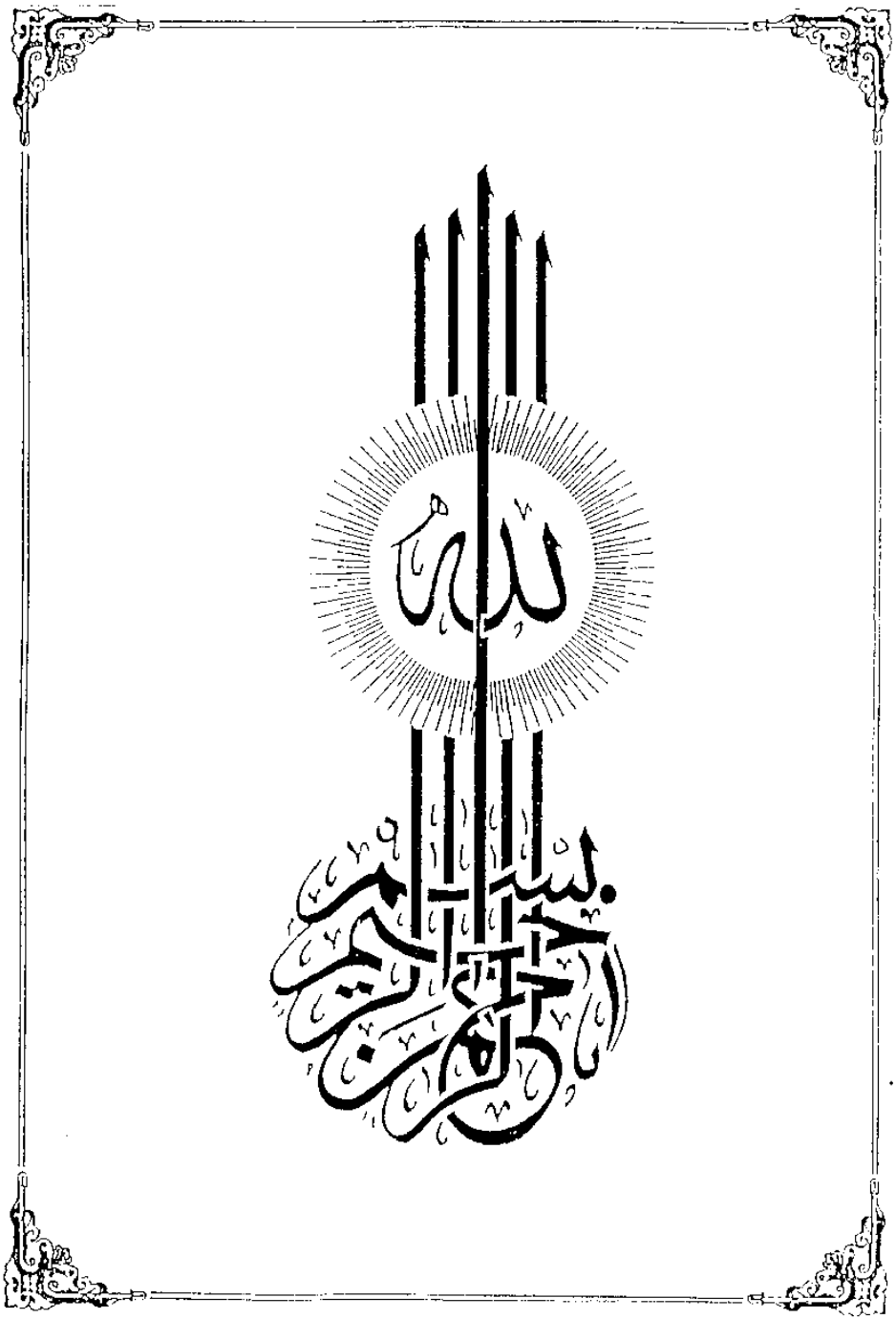

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CONTENTS

ABBREVIATIONS

ADP : Adenosine diphosphate.

A.H.F. : Antihaemophilic factor (F VIII/AHF, F VIII/C).

ATP : Adenosine triphosphate.

CRF : Chronic renal failure.

Cyclic AMP : Cyclic adenosine monophosphate.

DDAVP : 1-desamino-8-D-arginine vasopressin.

F VIII/AGN : Factor VIII - related antigen (F VIII R : Ag)

F VIII/AHF : Factor VIII - antihaemophilic factor (F VIII/C).

F VIII/C : Factor VIII - procoagulant activity (AHF).

F VIII R : Ag : Factor VIII - related antigen.

F VIII/VWF : Factor VIII - Von Willebrand activity.

GPI : Glycoprotein I.

mol. wt. Molecular weight.

PF_3 : *Platelet factor 3.*

PGI_2: *Prostacyclin.*

PTT : Partial Thromboplastin time.

Tx A_2: *Thromboxane* A_2.

V.W.D. : Von Willebrand's disease.

V.W.F. : Von Willebrand factor (F VIII/VWF).

INTRODUCTION
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INTRODUCTION :

The presence of bleeding tendency in patients with chronic uremia is well recognized and contributes to their morbidity and mortality. Extensive investigations have failed to identify with certainity the exact cause of bleeding tendency in chronic renal failure. It is generally believed that qualitative and/or quantitative platelet abnormalities are the most significant factors in the pathogensis of uremic bleeding (Rabiner; 1972).

It was previously reported that 1-deamino-8-D-arginine vasopressin (D.D.A.V.P) - a synthetic analogue of the antidiuretic hormone, 8 arginine vasopressin - infusion shortens the bleeding time in uremics possibly by mechanisms other elevation of factor VIII/Vonwillebrand factor (Carvalho; 1983).

The effect of D.D.A.V.P on bleeding time could be secondary to its effect on the vessel wall or the platelet quality and/or quantity. This latter cause will be the concern of this study which may be of help later on in controlling bleeding in those patients.

AIM OF THE WORK :

The aim of this work is to find out the effect of D.D.A.V.P on platelet quality and quantity in cases of chronic renal failure with bleeding tendency.

REVIEW OF LITERATURE

Chapter I

BLEEDING IN UREMIA

Numerous hemostatic abnormalities have been associated with acute and chronic renal disease. The most common abnormalities are defective platelet aggregation, decreased platelet adhesiveness, decreased platelet factor-3 availability, and prolongation of the bleeding time. Among the above platelet function tests, the bleeding time is the single test that most closely correlates with clinical bleeding. (Jubelirer, 1985)

The nature of the platelet defect in uremia is still not well understood. The pathophysiologic mechanisms which have been implicated include platelet inhibition by plasma metabolites, e.g, urea, guanidonsuccinic acid, phenolic acid, increased vessel wall prostacyclin, abnormal platelet arachidonic acid metabolism, increased level of parathyroid hormone (P.T.H), defective binding of the factor VIII complex to platelet or defective binding of platelets to vessel wall subendothelium by the factor VIII complex, decreased platelet vessel wall interaction due to severe anaemia, platelet storage pool deficiency, and/or defective fibrinogen binding to platelets (Jubelirer, 1985).

Hyperparathyroidism and Platelets in Chronic Renal Failure :

The most significant complication of elevated parathyroid hormone levels in uremia is the development of osteitis fibrosa cystica a condition which leads to depression of bone marrow. The hormone also appear to play a role in soft tissue and organ calcification, metabolic abnormalities (glucose, lipids), and electroencephalographic changes seen in uremic patients. It role in haematological abnormalities of uremia (anaemia, bleeding) is contraversial. A role for parathyroid hormone in heart and skeletal muscle dysfunction in uremia has not been clearly established (Klahr-S, Slatopolsky-E, 1986).

Thus, parathyroid hormone may participate in the genesis of anaemias in uremia through at least three pathways; these include inhibition of erythropoiesis, shortening of survival of R.B.Cs and inducing fibrosis of bone marrow cavity. A possible fourth mechanism through which P.T.H may contribute to the anaemia of uremia is its effect on platelets. (Massry-S.G., 1983)

Parathyroid hormone inhibits platelet aggregation and, as mush,,may play an important role in the genesis of bleeding tendencies and the consequent blood loss in uremia (Massry-S.G., 1983).

In another way, parathyroid hormone raises intracellular cyclic A.M.P levels through adenyl cyclase activation and stimulates Ca^{++} transport across cell membranes. Since parathyroid hormone levels are markedly increased in uremic plasma, it might contribute to the defective platelet function, and the bleeding tendency frequently occurring in uremic patients (Benigni et al., 1985).

As parathyroid hormone depresses the bone marrow in uremic patients leading to that haematological abnormality including thrombocytopenia in those patients (Klahr,and Salatopolsicy-E, 1986). It was initially assumed that thrombocytopenia, with its concomitant haemorrhagic diathesis, was a common cause of uremic bleeding (Altschuler et al., 1960), and also it was thought to be an important contributing cause of death (Kalhr et al., 1957). But, although a mild thrombocytopenia may be present in some patients with renal failure, it is not a quite sufficient reason to account for bleeding abnormality (Castaled et al., 1966), as qualitative platelet abnormality is the most significant factor in the pathogenesis of uremic bleeding (Rabiner, 1972).

Blood Vessels and Platelets in Chronic Renal Failure :

It was also found that the subendothelial surface covered by platelets was significantly decreased in experiments with uremic whole blood when compared to normal controls. the interaction of platelets with subendothelium was also decreased when perfusions were carried out with platelet-plasma mixtures contains either normal washed platelets or uremic washed platelets. This shows an impaired platelet adhesion caused by a platelet and a plasmatic abnormality. (Castillo-R et al., 1985)

So, there is a defective platelet adhesion to subendothelium in uremic patients, caused by platelet and plasmatic alterations that are influenced by locohematocrit.(Castillo-R et al., 1986)

This finding supports what was said before regarding the haemorrhagic diaesthesis in uremia which is probably due to capillary fragility (Kuhlblack, 1957).

Another factor related to vessel wall endothelium is prostacyclin ($PG-I_2$), a recently discovered hormone, which is generated from prostaglandin endoperoxides by vessel wall endothelium, particularly in the lungs, and also in the kidenys. It is the most potent inhibitor of platelet aggregation so far described (Ylikorkala et al., 1982).

The endogenous antagonist of PG-I_2 is thromboxane A_2 (Tx A_2), generated by the platelets (Hamberg et al., 1975).

A balance between these two prostanoids may regulate platelet aggregation at least locally in the blood vessel walls (Ylikorkala et al., 1982).

Prostaglandin metabolism in platelets and in the vessel wall from uremic patients is impaired in different ways, both contributing to the impaired primary haemostasis in these patients (Remuzzi et al., 1978 c).

In uremic venous tissues, there is increased prostacyclin activity. It might be one of the non-dialyzable factors said to contribute to the impaired haemostasis in chronic renal failure (Remuzzi et al., 1977 a).

The capacity of uremic platelets to produce thromboxane A_2 is also decreased. This might result from decreased endoperoxide stores and could provide an additional explanation for the haemorrhagic diathesis seen in uremia (Yolikorkala et al., 1982).

Impaired platelet arachidonic acid metabolism also affects platelet aggregation in chronic uremia contributing to another