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Decreased Antithrombin III: is it A Cause or a Result of Oesophageal Varices Bleeding in Endemic Hepatic Schistosomiasis

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Abstract

Chronic liver disease is often associated with many haemostatic abnormalities including decreased level of antithrombin III (ATIII). However, the involvement of ATIII, in oesophageal varices bleeding has not been demonstrated before. The aim of this study is to demonstrate the haemostatic abnormalities especially the disturbance in ATIII level in patients with bleeding oesophageal varices. Forty subjects were studied including 10 normal control cases ,15 cases with bleeding oesophageal varices (group I) and 15 cases with silent varices (group II). All cases were subjected to the following haemostatic tests: prothrombin time (PT) partial thromboplastin time (PTT), antithrombin III level, fibrinogen (F) and fibrin degradation products (FDP). All these tests were done to patients of group I, the first during the bleeding episode (Ia) and the second after control of bleeding by two weeks (Ib). There was significant deterioration in all the haemostatic parameters studied in both group I and II compared to control. Further significant impairment in some of these parameters namely PT, AT III, FDP and platelet count occurred in patients of group I during active bleeding (Ia) compared to silent varices patients (group II). Most of these test differences disappeared after control of bleeding by two weeks with the exception of ATIII, which was still significantly lower in group Ib compared with group II ($p < 0.005$). We conclude that ATIII might be of great value to predict hepatic patients prone to bleed through their oesophageal varices. Further prospective studies are needed.

Introduction

CHRONIC liver disease is often associated with many haemostatic abnormalities. Over 85% of these patients have one or more abnormality in coagulation tests in platelet count and function and in fibrinolysis [1].

Bleeding of oesophageal varices has been attributed to portal hypertension. However, this bleeding may be exaggerated by the already present haemostatic abnormalities in this group of patients [2]. Antithrombin III is known to diminish in cirrhotic patients either due to diminished synthesis or increased consumption due to intravascular coagulation [3]. However,. the involvement of antithrombin III in bleeding of oesophageal varices has not been demonstrated (Cambridge Compact Medline Database, 1991).

The aim of this work is to demonstrate the haemostatic abnormalities especially the antithrombin III level during and after bleeding episodes in patients with oesophageal varices.

Material and Methods

This study was performed in Kasr El Aini Hospital. Forty subjects were selected (thirty cirrhotic patients and ten normal control persons). The former were 15 patients with bleeding oesophageal varices (group I) and 15 with silent varices (group II). None of these patients or the control cases had received medications that may have any effect on coagulation, fibrinolytic or platelet functions. All cases were subjected to routine clinical examination, liver function tests complete blood count, abdominal ultrasonography, gastrointestinal endoscopy beside the following haemostatic tests:

(1) Prothrombin time (PT) [4].

(2) Partial thromboplastin time (PTT) [5].

(3) Antithrombin III by radial immunodiffusion plates [6].

(4) Fibrinogen by radial immunodiffusion plates [7].

(5) Fibrin degradation products (FDP) by staphylococcal clumping test [8].

The haemostatic tests and complete blood count were done twice to patients of group I, the first during the bleeding episode (Ia) and the second after control of bleeding by 2 weeks (Ib).

Statistical Methods:

Using Mean ± S.D. Student (t) test and the probability (p) for comparison.

Results

All patients had positive history of intestinal schistosomiasis, while only (40%) of patients in each of group I and II gave history of viral hepatitis. Clinical examination did not disclose any significant difference in clinical findings between group I and II. There was no significant difference in the grade of oesophageal varices between these 2 groups. Liver enzymes and serum albumin were not statistically different between the 2 groups. The results of the different haemostatic parameters in the

Table (1) : Different Haemostatic Parameters in Different Groups Studied.

	Control (10)	Group Ia (15)	Group Ib (15)	Group II (15)	*p* 1 <	*p* 2 <	*p* 3 <	*p* 4 <	*p* 5 <	*p* 4 <
PT (sec)	12.8 : 3.8	22.3 : 4.7	17.72 : 3.43	17.3 : 2.7	0.001	0.005	0.002	0.05	0.01	NS
PTT (sec)	27.6 : 3.45	61.9 : 21.26	54.15 : 18.1	45.2 : 12.76	0.002	0.002	0.005	NS	NS	NS
ATIII (μg/mL)	30.1 : 2.8	7.85 : 2.9	10.33 : 3.75	17.45 : 4.00	0.001	0.001	0.001	0.05	0.001	0.05
Fibrinogen g/L	3.05 : 0.3	1.74 : 0.17	1.88 : 0.15	2.75 : 0.39	0.001	0.001	0.002	NS	NS	NS
FDP (μg/ml)	2.55 : 1.42	15.95 : 9.3	10.0 : 2.5	7.8 : 3.27	0.001	0.001	0.002	NS	0.05	NS
Platelet count $X10^3$/cmm	228.1 :	104 : 3.94	117.5 : 4.3	145.25 : 14.39	0.001	0.005	0.001	NS	0.02	NS

Abbreviations:
PT = Prothrombin time.
PTT = Partial thromboplastin time.
P1 = Group Ia (during bleeding) versus control.
FDP = Fibrin degradation products.
P2 = Group Ib (after control of bleeding) versus control.
P3 = Group II (silent varices) versus control.
P4 = Group Ia (during bleeding) versus group Ib (same after control of bleeding).
P5 = Group Ia (during bleeding) versus group II (silent varices).
P6 = Group Ib (after control of bleeding) versus group II (Silent varices).
N.S. = Non significant.
All data are presented as mean ± S.D.

different groups are shown in table 1.

There was a significant difference in prothrombin time, partial thromboplastin time, antithrombin III level, fibrinogen level, fibrin degradation products level and platelet count between control subjects and both group I and II. There was a significant prolongation in prothrombin time (22.3, 17,72 and 17.3 seconds in group Ia, Ib and II compared to control value, 12.8 sec. p <0.001, <0.005 and <0.002 respectively), prolongation of partial thromboplastin time (61.9, 54.15 and 45.2 seconds in group Ia, Ib and II compared to control value 27.6, p <0.002 , <0.002 and <0.005 respectively).

As regards antithrombin III level, there was significantly lower values in group Ia, Ib and II (7.85, 10.33 and 17.45 μg/ml respectively) compared to the normal control

value of 30.1 μg/ml, $p < 0.001$ for all the three groups.

Fibrinogen and fibrin degradation products were abnormal. The former was significantly lower ($p < 0.001$, < .001 and <0.002) and the latter was significantly higher ($p < 0.001$, < 0.001 and < 0.002 in group I, and II respectively) compaed to the control group.

Platelet count was significantly reduced in group Ia. Ib and II compared to control group, ($p < 0.001$, < 0.005 and < 0.01 respectively).

Comparing groups Ia (patient during active bleeding varices) with Ib (same patients 2 weeks after control of the prothrombin time during bleeding episode (22.3 vs 17.27 respectively) $p < 0.05$ with significant decrease in antithrombin, III level (7.85 vs 10.33 μg/L) $p < 0.05$.

compared with patients of group II (silent vaices) patients during active bleeding (Ia) showed significant prolongation in prothrombin time (22.3 vs 17.3 second, $p < 0.01$), significant reduction in AT (III) (7.85 vs 17.45 μg/ml, $p < 0.001$), significant increase in fibrin degradation products (15.95 vs 7.8 μg/ml, $p < 0.001$), significant increase in fibrin degradation products (15.95 vs 7.8 μg/ml , $p < 0.05$) and significant decrease in platelet count (104×10^3 vs 145×10^3/ cm, $p < 0.02$).

Antithrombin III level was the only parameter showing a significantly lower level in patients recovering from active variceal bleeding when compared to those with silent varices (10.33 vs 17.45 μg/ml, $p < 0.005$).

Discussion

Bleeding tendency in patients with chronic liver disease is attributed to many factors namely deficient synthesis of coagulation factors by the diseased liver, increased fibrinolytic activity and platelet quantitative and qualitative defects [8].

The cirhotic patients of either group I or II included in this study showed deterioration in all the haemostatic parameters studied namely PT, PTT, AT III, fibrinogen, FDP and platelet count. Further impairment in some of these parameters namely PT, AT III, FDPs and platelet count was observed in patients during active bleeding (group Ia) compared to patients with silent varices (group II). Consumption of the different clotting factors and platelets during active bleeding episode would explain this significant further haemostatic deterioration in the bleeder group during the active bleeding episode.

Most of the differences between group Ia and II disappeared 2 weeks after control of bleeding with the exception of antithrombin III showing "highly significant lower levels in group Ib compared to group II.

The persistent decrease in antithrombin III levels in the bleeder group (Ib) two weeks after the active oesophageal bleeding might be due to slowed synthesis or continued consumption. The slowed synthesis seems unlikely because other coagulation

factors involved in both extrinsic and intrinsic pathways of coagulation (tested by prothrombin time and partial thromboplastin times respectively) in addition to fibrinogen have returned to levels insignificantly different from those of non bleeders (group II), see table. Moreover, the insignificant difference in fibrin degradation products levels between both of group Ib and group II could obviate continued consumption as an explanation for the persistent decreased antithrombin III levels. Therefore, it seems likely that cirrhotic patients vulnerable to bleeding oesophageal varices have already deranged antithrombin III synthetic pathway giving rise to this difference between bleeders and non bleeders. During active bleeding, antithrombin III levels furtherly drop significantly ($p < 0.05$) denoting increased consumption at that time returning back to the lower pre-bleeding levels possibly characteristic of this group of bleeders.

If this conclusion is going to be supported by further prospective studies in cirrhotic patients with portal hypertension regular estimation of antithrombin III would be of great value to predict those hepatic patients who are prone to bleed through their silent varices.

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