Evaluation of Haemostatic Changes among Gastrointestinal Bleeding Patients with Portal Hypertension and Liver Cirrhosis attending Ibn Sina Teaching Hospital (Sudan)

Shatha E. El Magzoub¹, Ahmed S. Mohamed¹, Sara A. Mohamed¹, Ibrahim K. Ibrahim²
¹Sudan International University, Khartoum, Sudan
²Al -Neelain University, Khartoum, Sudan

Abstract

Background: Substantial changes in the haemostatic system may occur among gastrointestinal bleeding patients with chronic liver diseases such as portal hypertension, liver cirrhosis, hepatitis and cancer. The liver plays a vital role in the hemostatic system as it synthesizes the majority of coagulation factors and anticoagulant proteins involved in the process of fibrinolysis. Also, the liver produces thrombopoietin, which is responsible for platelet production from megakaryocytes.

Objective: To evaluate the haemostatic changes among gastrointestinal (GI) bleeding patients with portal hypertension and liver cirrhosis attending Ibn Sina Teaching Hospital (Sudan).

Materials and methods: The study population were patients with acute gastrointestinal bleeding attending the emergency unit of Mohammed Salih Idris Centre for acute GI bleeding. 70 samples were collected from these patients (test group), and 50 samples were collected from age- matched healthy individuals (control group). 2.5 ml venous blood were collected from each participant in ethylene diamine tetra acetic acid (EDTA) containers for platelet count and 1.8 ml venous blood were collected in tri- sodium citrate containers and platelet- poor plasma was prepared for analysis of fibrinogen, prothrombin time (PT) and activated partial thromboplastin time (APTT).

Results: The mean PT (17.66 ± 4.96 seconds) and APTT (43.87 ± 16.80 seconds) were found significantly higher among the test group patients than the control group patients (p = 0.000 for both PT and APTT). The mean platelets count (170.8 ± 126.3x10⁹/L), the mean fibrinogen level (191.16 ± 110.40 mg/dl) was significantly low among test group patients as compared with the control group patients (p = 0.000). The study found a significant association between fibrinogen level and platelet count (p = 0.001), and PT level (p = 0.004). There was no significant correlation between fibrinogen level and APTT level (p = 0.06).

El Magzoub, et al., 2018: Vol 3 (10)
Conclusion: Haemostatic changes were verified by the lower fibrinogen level, lower platelets count, prolonged PT, and prolonged APTT among the test group patients as compared with the control group participants.

Key words: Haemostatic changes, GI bleeding, Portal hypertension, Liver cirrhosis.

Introduction

Chronic or acute liver diseases frequently have a profound impact on the hemostatic system. An important factor contributing to the coagulation disturbances in liver disease is the decreased plasma levels of hemostatic proteins synthesized by the liver. In addition, thrombocytopenia as a result of decreased platelet production or increased platelet turnover and intravascular activation of hemostasis resulting in consumption of hemostatic factors contributes to alterations in the hemostatic system. Furthermore, continuous low-grade activation of endothelial cells results in continuous release of several hemostatic proteins which levels are therefore frequently elevated in patients with liver disease, e.g. von Willebrand factor (VWF). Finally, portal hypertension, a common complication of chronic liver failure, results in hemodynamic changes that may impact endothelial function. Moreover, portal hypertension results in splenomegaly, which in turn results in increased platelet sequestration in the spleen.

Hepatic diseases are associated with a variety of defects affecting both primary and secondary hemostasis. It is therefore not surprising that advanced hepatic disease is associated with bleeding. Chronic liver disease frequently causes portal hypertension with resultant hypersplenism and thrombocytopenia. This leads to formation of fragile vascular anomalies (varices) that may bleed profusely on a background of hemostatic failure.

This study aimed to find out the first line investigation of hemostasis and fibrinogen level in hepatic portal hypertension and liver cirrhosis.

Materials and methods

This was a comparative, cross-sectional, control study. The study population were patients with acute gastrointestinal bleeding attending the emergency unit of Mohammed Salih Idris Centre for acute GI bleeding at Ibn Sina Teaching Hospital (Sudan). The study was conducted during the period from August-September 2016. Informed, verbal consent was taken from each patient prior to specimen collection. The study was approved by the Research and Training Committee at Ibn Sina Hospital. Confidentiality of information regarding patients investigated was maintained. Permission to collect the specimens was obtained from the authorities of Ibn Sina Teaching Hospital. All participants were interviewed and data was collected in structured questionnaire. The study results were analyzed by the Statistical Package for Social Sciences (SPSS) version 20. The Pearson's chi-square test was used to assess intergroup significance, and t-test was used to determine differences in means. Other variables, frequencies, and odd ratio were calculated and presented in form of figures and tables. The probability value and odd ratio were used to
assess the significance of the study findings. A p-value less than 0.05 was considered significant. 70 samples were collected from these patients (test group), and 50 samples were collected from age-matched healthy individuals (control group). 2.5 ml venous blood were collected from each participant in ethylene diamine tetra acetic acid (EDTA) containers for platelet count and 1.8 ml venous blood were collected in tri-sodium citrate containers and platelet-poor plasma was prepared for analysis of fibrinogen, prothrombin time (PT) and activated partial thromboplastin time (APTT). Platelet count and indices were measured using a full automated haematology analyzer (Sysmex KX -21N, Japan). Determination of prothrombin time (PT) and activated partial thromboplastin time (APTT) were analyzed by a coagulometer (Coatron M2). The clotting time of plasma was analyzed in the presence of an optimal concentration of tissue extract (thromboplastin), cephalin, and kaolin and the kaolin cephalin clotting time (KCCT) in presence of calcium chloride (CaCl₂). Fibrinogen concentration was measured by the Clauss method according to manufacturer's instructions (Helena Biosciences Europe, UK).

Results

According to type of disease, the patients investigated were divided into 5 groups: 44 patients (62.9%) with esophageal varices, 18 patients (25.7%) with peptic ulcer, 5 patients (7.1%) with liver cirrhosis, one patient (1.4%) with Hepatitis C virus, and 2 patients (2.9%) with other GI bleeding conditions. Also, the predominant cases of GI bleeding was among patients aged 36-67 years with median age of 51.6 years. As shown in Table (1), the mean PT (17.66 ± 4.96 seconds) and APTT (43.87 ± 16.80 seconds) were found significantly higher among the test group patients than the control group patients (p = 0.00 for both PT and APTT). Also, the mean platelets count (170.8 ± 126.3x10⁹/L), the mean fibrinogen level (191.16 ± 110.40 mg/dl) was significantly low among test group patients as compared with the control group patients (p = 0.00). Also there was no significant association between fibrinogen level and platelets large cell ratio (p = 0.139) and mean platelet volume (p = 0.758). However, there was a significant association with platelets distribution width (PDW) among test group patients as compared with control group participants (p = 0.003). The mean of PT (17.66 ± 4.96 seconds) and APTT (43.87 ± 16.80 seconds) were significantly higher among patients than the controls (p-value 0.000 for each parameter).

Mean platelets count (170.8 ± 126.3X10⁹/L), mean fibrinogen level is (191.16 ± 110.40mg/dl), and were significantly low among patients when compared with the controls (p. value 0.000). On the other hand, and as shown in Table (2), the study found a significant association between fibrinogen level and platelet count (p = 0.001), and PT level (p = 0.004). There was no significant correlation between fibrinogen level and APTT level (p = 0.06).

El Magzoub, et al., 2018: Vol 3 (10)
Table (1): Haemostatic changes among test group patients as compared with control group participants

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test group (70 patients)</th>
<th>Control group (50 participants)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>170.8 ± 126.3</td>
<td>313.6 ± 56.5</td>
<td>0.00</td>
</tr>
<tr>
<td>P-LCR</td>
<td>26.9 ± 6.4</td>
<td>24.3 ± 7.5</td>
<td>0.139</td>
</tr>
<tr>
<td>MPV</td>
<td>9.96 ± 0.97</td>
<td>9.88 ± 0.94</td>
<td>0.758</td>
</tr>
<tr>
<td>PDW</td>
<td>14.21 ± 2.80</td>
<td>12.38 ± 2.19</td>
<td>0.003</td>
</tr>
<tr>
<td>PT</td>
<td>17.66 ± 4.96</td>
<td>14.4 ± 0.95</td>
<td>0.00</td>
</tr>
<tr>
<td>APTT</td>
<td>43.87 ± 16.80</td>
<td>31.20 ± 3.19</td>
<td>0.00</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>191.16 ± 110.40</td>
<td>290.92 ± 56.25</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Table (2) Correlation of fibrinogen level with platelets count, PT, INR and APTT

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal fibrinogen (18 samples)</th>
<th>Abnormal fibrinogen (45 samples)</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>106.94 ± 62.782</td>
<td>198.47 ± 144.117</td>
<td>0.001</td>
</tr>
<tr>
<td>PT</td>
<td>21.439 ± 6.4318</td>
<td>16.193 ± 3.4151</td>
<td>0.004</td>
</tr>
<tr>
<td>INR</td>
<td>1.5633 ± .11170</td>
<td>1.4327 ± .28813</td>
<td>0.50</td>
</tr>
<tr>
<td>APTT</td>
<td>51.39 ± 19.443</td>
<td>41.03 ± 15.732</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Discussion
Haemostasis is intimately related to liver functions, because most coagulation factors are synthesized in liver parenchymal cells; and the liver's reticuloendothelial system serves an important role in the clearance of activation products. The extent of coagulation abnormalities depends upon the degree of disturbed liver function. The ultimate goal in caring for a patient with liver cirrhosis is to prevent bleeding before it occurs. Oesophageal varices were the predominant cause of bleeding resulting from hepatosplenic *Schistosoma mansoni* infection. This infestation has a prevalence rate of 52%- 89% among workers of Geiza Irrigation Scheme.

*El Magzoub, et al., 2018: Vol 3 (10)*
This prevalence rate is considered very high when compared with counterparts in other endemic areas such as Egypt where the prevalence rate is 17.5%-42.9%\(^4\). Both age and grade of fibrosis are associated with regression of periportal fibrosis (PPF). The fact that low fibrosis grades are responsive to praziquantel treatment could be due to the nature of the content of the fibrosis tissue. This could be due to the collagen content that might have not undergone cross-linking, which usually stabilizes the tissue against fibrinolysis. Periportal fibrosis in younger patients is mostly at an earlier stage, which may explain why PPF is more reversible at a younger age\(^5\).

This study evaluated the haemostatic changes in GI bleeding patients. The levels of fibrinogen, PT, APTT, and the platelets count were analyzed in 70 patients, and compared with the control group participants. The mean PT (17.66 ± 4.96 sec) and the mean APTT (43.87 ± 16.80 sec) were significantly higher among test group patients than the control group participants. This finding was similar to the findings reported by research workers in Sudan\(^6\).

Also, the mean platelets count (170.8 ± 126.3 x 109/L) and the mean fibrinogen level (191.16 ± 110.40 mg/dl) were significantly low among test group patients as compared with control group participants (p = 0.00). The low platelets count was due to impaired production of thrombopoietin in liver disease. This results in reduced platelet production by mega-karyocytes in the bone marrow. Thrombocytopenia is a common finding in advanced liver disease. It is a predominant result of portal hypertension and platelet sequestration in the enlarged spleen\(^5\).

Fibrinogen is synthesized at the level of the hepatic microsomes and the existence of multiple coagulation defects, including PT prolongation with normal or high fibrinogen levels has been frequently observed in patients with severe liver disease\(^6\).

There was a significant association between fibrinogen level and platelet count (p = 0.001), PT (p = 0.004), and APTT (p = 0.005) There is no significant association between fibrinogen level and APTT (p = 0.07). These findings were similar to the findings of a study conducted among patients with liver disease by Shah and his co-workers\(^7\) who reported a significant association (p < 0.05) between PT, APTT, and platelet count in patients of liver cirrhosis.

**Conclusion:** Haemostatic changes were verified by the lower fibrinogen level, lower platelets count, prolonged PT, and prolonged APTT among the test group patients as compared with the control group participants.

**Conflict of interests:** No conflict of interest was declared.

**Acknowledgments:** We would like to thank all patients and participants involved in the study. Special thanks go to all staff of Ibn Sina Teaching Hospital and Mohammed Salih Idris Centre for Acute GI Bleeding, Khartoum, Sudan.

**References**


**El Magzoub, et al., 2018: Vol 3 (10)**
4. Records of Ibn Sina Teaching Hospital, Khartoum, Sudan. 2015.

El Magzoub, et al., 2018: Vol 3 (10)