FREQUENCY OF THROMBOCYTOPENIA; PATIENTS WITH CHRONIC HEPATITIS C INFECTION

Dr. Zunaira Nawaz, Dr. Muhammad Aurangzeb, Dr. Khalid Imran, Dr. Tazeen Rasheed, Dr. Muhammad Tanveer Alam, Dr. Mehwish Fatima Jaffery, Dr. Shumaila Khero, Prof. Muhammad Masroor

ABSTRACT... Objective: To determine frequency of thrombocytopenia in patients with Chronic Hepatitis C infection. Methods: A 6 months cross sectional study was carried out to determine frequency of thrombocytopenia in all patients admitted with chronic hepatitis c infection in all medical units at Civil Hospital Karachi, from April 2, 2012 to October 1, 2012. Patients with platelet count <150,000/microL was labeled as having thrombocytopenia and categorized according to the Child-Pugh Scoring. Patients with Child-Pugh score <7 was categorized in Grade A, 7-9 in Grade B and >9 in Grade C. Results: Out of 141 patients, 46(32.6%) were male and 65(46%) were female with 1.17:1 male to female ratio. The average age of patients was 47.25 ± 11.52 years (95%CI: 45.33 to 49.17). Similarly average duration of illness was 3.06 ± 1.78 Years (Range 8 months to 9 Years) and average platelet count was 165156.74± 176324.9. Seventy five patients (53%) had thrombocytopenia (platelet count <150000/microL). The average age of thrombocytopenic patients was 48.53±12.34 years and duration of illness was 3.7 ± 1.81 years. Regarding child Pugh class, 35(24.8%) cases had in class A, 49(34.8%) in class B and 57(40.4%) in class C. Thrombocytopenia was most common in above 60 years of age that is 10.7% (8/75) and 22.7% to 32% in all age groups. Conclusions: In our study the frequency of thrombocytopenia was found to be higher. Patients of age more than 60 years and of child-Pugh class C affected the most.

Key words: Chronic Hepatitis C (CHC), Thrombocytopenia, Child-Pugh Scoring.

INTRODUCTION

Hepatitis C virus (HCV) was first identified in 1989 as the causative agent of most cases of post transfusion and sporadic non-A, non-B hepatitis. According to WHO statistics, the global prevalence of HCV is 3.1% (lower in Europe 1.03% and Americas 1.7%) and highest in Africa 5.3%2. Chronic Hepatitis C (CHC) infection is a serious health problem in Pakistan with prevalence rate of about 4-6%3. Hepatitis C virus infection has become a global health and socio-economic problem as 60% to 85% of infected persons develop chronic liver disease3. Thrombocytopenia (platelet count <150,000/microL) is a common complication in patients with chronic liver disease (CLD) that has been observed in up to 76% of patients. Moderate thrombocytopenia (platelet count, 50,000/microL-75,000/microL) occurs in approximately 13% of patients with cirrhosis4.

Thrombocytopenia in HCV infection has been known since 19935. The development of thrombocytopenia in patients with chronic liver disease due to CHC infection is complex and multifactorial6. In patients with untreated hepatitis C, both prevalence and severity of thrombocytopenia increase in parallel with the severity of disease, usually becoming clinically relevant when patients develop extensive fibrosis and cirrhosis. Pathogenetic mechanisms include hypersplenism secondary to portal hypertension5,6, aberrations of the immune system resulting in the formation of anti-platelet antibodies and/or immune-complexes that bind to platelets and facilitate their premature clearance, development of immunologically-mediated
extrahepatic manifestations including mixed cryoglobulinemia with or without associated joint, renal, or cutaneous involvement, and thrombopoietin (TPO) deficiency secondary to liver dysfunction\(^6\), bone marrow suppression resulting from either HCV itself or interferon treatment. The observation that, thrombocytopenia is more severe in cirrhotic patients than non cirrhotics indicates additional factors to its pathogenesis\(^3,5\). TPO levels are significantly low in cirrhotic patients\(^8\) as compared to chronic hepatitis patients\(^8\) indicating impaired production\(^6\) or rapid degradation of thrombopoietin\(^8\). Rios et al showed that TPO levels were related to the splenic size with its levels rising after partial splenic embolization\(^9\). The incremental effect of Eltrombopag (thrombopoietin-receptor agonist) on platelet count in patients with thrombocytopenia due to HCV-related cirrhosis reaffirms the role of TPO\(^10\). In a study from Pakistan frequency of thrombocytopenia (platelet count<150,000) was 32.2% in patients with chronic liver disease (CLD) due to HCV\(^8\). Another study from Taiwan showed that 10.2% patients had platelet count of <100,000/mm in patients with positive anti HCV antibody\(^11\).

Thrombocytopenia in CLD due to HCV is important, not merely as an association but because it has been proposed as a significant predictive indicator of esophageal varices in HCV patients\(^12\).

The aim of this study is to evaluate the burden of thrombocytopenia in Chronic Hepatitis C infection. This study will be helpful in planning further treatment strategies in patients with CHC infection to prevent bleeding complications like hematemesis, malena etc.

**MATERIAL & METHODS**

This study was conducted at All medical Units of Civil Hospital Karachi, from April 2, 2012 to October 1, 2012. Patient’s age > 20 years with Chronic Hepatitis C infection, diagnosed by Anti HCV +ve by ELIZA (4th generation, cut off: >0.328) admitted in Medical Units at Civil Hospital Karachi fulfilling the inclusion criteria were included in this study. On the day of admission, after getting informed verbal consent from the patients, Researcher took detailed history regarding duration of illness and did clinical examination for severity assessment. 10cc blood collected after informed consent on the same day and sent to same laboratory to minimize bias for Platelet count, PT (Prothrombin Time) INR, Serum Albumin, LFT (Liver Function Test) to detect thrombocytopenia and severity of Chronic Hepatitis C according to Child-Pugh scoring (attached as annexial). Patients with platelet count of <150,000 was labeled as having thrombocytopenia and was categorized according to the Child-Pugh scoring. Patients with Child-Pugh score <7 categorized in Grade A, 7-9 in Grade B and >9 in Grade C. Inclusive criteria patients were 20 years of age, CHC patients of >6months duration, both male & female. Exclusion criteria were age less than 20 years, CLD patients with both Anti HCV & Hep Bs Ag +ve, patient with recent history of febrile illness and patients with significant drug history that is known to cause thrombocytopenia like interferon etc.

**RESULTS**

A total of 141 chronic hepatitis C infected patients were included in this study. Most of the patients were 31 to 60 years of age that is 85.1% and distribution of age are presented in figure 1. The average age of the patients was 47.25 ± 11.52 years. Similarly average duration of illness was 3.06 ± 1.78 Years (Range 8 months to 9 Years) and average platelet count was 165156.74± 176324.9.

Out of 141 patients, 46(32.62%) were male and 65(46%) were female with 1.17:1 male to female ratio as presented in Table I. Duration of illness of the patients is presented in table I. Minimum duration of illness was 8 months while maximum duration of illness was 9 Years. Duration of illness of 10 patients (7.1%) was below one years, 85(60.3%) had tolerated disease from 1 to 3 years, 37(26.2%) cases tolerated from 4 to 6 years and 9(6.4%) had tolerated disease 7 to 9 years.
Frequency of thrombocytopenia in patient with chronic hepatitis C is presented in Table-I. Seventy five patients (53%) had thrombocytopenia (platelet count <150000/microL). The average age of thrombocytopenic patients was 48.53±12.34 years and duration of illness was 3.7 ± 1.81 years. Regarding child Pugh class, 35(24.8%) cases had in class A, 49(34.8%) in class B and 57(40.4%) in class C.

Thrombocytopenia was most common in above 60 years of age that is 10.7%(8/75) and 22.7% to 32% in all age groups as presented in table II while thrombocytopenia was similar in male and female as shown in table I.

Rate of thrombocytopenia was linearly increased with respect to duration of illness as. Similarly severity of CHC according to child Pugh scoring, thrombocytopenia was commonly seen in class C that was observed in 62.7% (47) cases as presented in table-I.

**DISCUSSION**

Thrombocytopenia (platelet count <150,000/microL) is a common complication in patients with chronic liver disease (CLD) that has been observed in up to 76% of patients. Moderate thrombocytopenia (platelet count, 50,000/microL-75,000/microL) occurs in approximately 13% of patients with cirrhosis⁴.

The association between HCV infection and thrombocytopenia is unclear⁵ but hepatic fibrosis
might be central to it\textsuperscript{14}. The liver is the main site for the production of thrombopoietin, the dominant cytokine for controlling the development of megakaryocyte and platelet production\textsuperscript{15}. Thrombopoietin levels and platelet counts are highly correlated with liver-function impairment and the severity of hepatic fibrosis in chronic HCV infection \textsuperscript{8,14}. Chronic hepatitis C virus infection may be accompanied by a variable degree of thrombocytopenia caused by a central and/or a peripheral (autoimmune) mechanism. The HCV infection can exert its effects on thrombogenesis by either a direct suppressive effect on the bone marrow, reducing the megakaryocyte production, or it can have a direct effect on the megakaryocytes, leading to low platelet production\textsuperscript{16}. Weksler’s study shows that in chronic hepatitis C virus infected patients, without hypersplenism or evidence of antiplatelet autoantibodies, the alpha interferon therapy was followed by a significantly increased platelet number due to the considerable decrease in the viral load\textsuperscript{7}. However, interferon also has a direct myelosuppressive effect which in itself can lead to thrombocytopenia, attenuating some of the positive effects\textsuperscript{7}. Chronic alcohol abuse may be an additional factor, which contributes to medullary megakaryocyte inhibition\textsuperscript{17}. Other studies have shown increasing thrombopoietin levels and platelet counts after IFN therapy in patients with HCV infection\textsuperscript{18} or who have undergone liver transplantation\textsuperscript{19,20}. This indicates that thrombocytopenia in persons with HCV infection might be strongly associated with disease activity and long-term progression.

In our study seventy five patients out of 141 cases (53%) had thrombocytopenia (platelet count <150000/microL). Whereas in a local study published in 2009, Noorul Iman et al, found that fifty patients out of one hundred and fifty five (32.3%) had thrombocytopenia\textsuperscript{3}. In a study conducted in Tehran, the prevalence of thrombocytopenia was found to be 13.3% which was higher as compared to controls\textsuperscript{21}. Several studies have shown that thrombocytopenia is frequently observed in chronic hepatitis C\textsuperscript{22,23} and a variety of pathogenic mechanisms are reported to be implicated in this abnormal finding. In cirrhotic patients sequestration of platelets in the enlarged spleen secondary to portal hypertension can cause thrombocytopenia\textsuperscript{24}. However, thrombocytopenia also occurs in patients with chronic hepatitis C without cirrhosis. Another mechanism is autoimmune reaction to platelets\textsuperscript{25}. Some reports indicated that HCV infection may reflect the expression of platelets-associated immunoglobulin G (PAIgG) leading to platelets destruction by reticulo-endothelial system\textsuperscript{26}. In addition, several studies have suggested that HCV may have a direct pathogenic role in the process leading to thrombocytopenia\textsuperscript{27}. A study from Taiwan showed 10.2% had platelet count of <100,000/mm\textsuperscript{3} in patients with positive anti HCV antibody\textsuperscript{11}. The low frequency of thrombocytopenia in their study could be due to their definition of thrombocytopenia used. The definitions of thrombocytopenia varied between studies and were based either on platelet counts, with threshold levels ranging between ≤100×10\textsuperscript{9} and ≤180 ×10\textsuperscript{9}/L, or on criteria set in haematological guidelines. The prevalence of thrombocytopenia (TCP) ranged from 0.16% to 45.4% and more than half of the studies reported a TCP prevalence of 24% or more\textsuperscript{28}. Because of the different TCP definitions, heterogeneity in study design and insufficient data on study characteristics such as age, gender, HCV treatment rates and disease severity an overall summary estimate of TCP prevalence among patients with HCV was not feasible. However, the relatively large prevalence in the majority of the studies suggests that there may be a substantial number of HCV patients at risk of bleeding complications and reduced likelihood of successful HCV antiviral treatment\textsuperscript{28}. Studies have shown that there is a decreasing trend of platelet count with increasing fibrosis and cirrhosis among patients with chronic liver disease. Among these patients, the reduction in platelets is mainly caused by platelet destruction from splenic pooling, because of portal hypertension, and the decreased synthesis of thrombopoietin by the liver\textsuperscript{29}. However, in cases of HCV, the virus itself or other mechanisms can also lead to low platelets\textsuperscript{30}.
The proportion of mild thrombocytopenia (defined as a platelet count under 150,000/μl) is between 41-50% in patients with HCV infection, while severe thrombocytopenia (defined as a platelet count of less than 50,000/μl) is reported in 9-32% of patients. Otherwise, several reports from different countries, confirmed the high prevalence of HCV infection in patients with chronic thrombocytopenia. Thrombocytopenia is common in malaria, viral and bacterial infections; and megaloblastic anemia and is even suggested as a predictor of falciparum malaria in febrile patients. Therefore we excluded patients with febrile illness and reporting of peripheral smear films by a hematologist of more than five years of post fellowship experience, all the false thrombocytopenia cases were excluded to give a clear picture. This is one of the strength of our study.

The average age of the patients was 47.25 ± 11.52 years in our study. The Mean age was 43.58 years (range 15-80) in a similar local study. Although the mean age is somewhat similar to our study but the difference in the frequency of thrombocytopenia was due to the severity of Chronic hepatitis C as per child pugh class. Mean platelet count was 165156.74±176324.9/micro L (range 186000 – 32000) in our study whereas it was 215154/mm cubed (range 3000-484000/mm cubed) in a study conducted in Peshawar.

In our study proportion of thrombocytopenia was 60% in patients ≤ 30 years, 46.5% in age group between 31-40 years, 45.9% in age group of 41-50 years, 60% in age group of 51-60 years and 72.7% in patients of more than 60 years of age. In Wang et al’s study, older persons (≥65 years of age) are 4 times more likely than those in other age groups to have thrombocytopenia. Similarly in the Peshawar study it was observed that thrombocytopenia was higher (26.5%) in patients of more than 40 years as compared to ≤40 years (5.8%). We believe long-term exposure to hepatitis C infection may partially explain this increased relative risk. On the other hand, whether the increase in the prevalence of thrombocytopenia with age is due to the higher incidence of myelodysplasia, predominantly occurring in older patients, also needs further evaluation.

As far as gender is concerned the proportion of thrombocytopenia was 57.3% in males and 42.7% in females. Similary in the study conducted in Iran males were more effected than females. This supports the results of our study. Local study of Peshawar had no difference in proportion of thrombocytopenia among males and females. This could be due to small sample size in the study. Regarding child Pugh class, 35(24.8%) cases were of class A, 49(34.8%) were in class B and 57(40.4%) were in class C. it clearly shows that majority of the patients were of child pugh class C. In contrast to our study the study of Peshawar shows that there were 103(66.5%) patients in class A, 44(28.4%) were in class B and 8(5.2%) were in class C. most of the patients belonged to Child Pugh class A. This shows why there is difference in proportion of the thrombocytopenia in the two studies. In our study the proportion of the thrombocytopenia was higher 53% whereas it was 32.3% in the study of Noor-ul Iman.

CONCLUSIONS
In our study the frequency of thrombocytopenia was found to be higher. Patients of age more than 60 years and of child-Pugh class C affected the most.

Copyright© 15 May, 2014.

REFERENCES


---

“When you repeat a mistake, it is not a mistake anymore: it is a decision.”

Paulo Coelho