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ASSOCIATION THROMBOCYTOPENIA AND ITS CO-RELATION IN CHRONIC LIVER DISEASE PATIENTS IN A TERTIARY CARE HOSPITAL

General Medicine

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ABSTRACT

INTRODUCTION: The prevalence of thrombocytopenia varies according to a number of factors, like patient population and severity of underlying liver disease.

AIMS AND OBJECTIVES: To determine prevalence of thrombocytopenia in CLD patients and correlation of platelet count with child and pugh scores.

MATERIAL AND METHOD: General Medicine ward and OPD of N.R.S.M.C.H. , Kolkata, All patients admitted with CLD in Medicine ward and those attending OPD of N.R.S.M.C.H. , Kolkata, One year, 101 (one hundred and one)

CONCLUSION: We found that mean Platelet count was low in Severe Thrombocytopenia which was statistically significant.

KEYWORDS

Thrombocytopenia and CHRONIC LIVER DISEASE

INTRODUCTION

Thrombocytopenia (Platelet count < 1.5 Lakh/ microliter with sub-definitions 50-100,000/μL [moderate] and <50,000/μL [severe]) is a common complication[1] and most common hematological abnormality in patients with chronic liver disease(CLD) that has been observed in up to 76 % of patients[1]. Cirrhosis is characterized by a complete distortion of hepatic architecture with loss of liver cell function and impairment of liver circulation. Several factors contribute to thrombocytopenia, the major mechanisms include (1) platelet sequestration in the spleen; and (2) decreased production of thrombopoietin in the liver[2].

The prevalence of thrombocytopenia varies according to a number of factors, like patient population and severity of underlying liver disease[3].The prevalence of thrombocytopenia in patients with chronic hepatitis has been reported to be only 6%, but occurs in up to 78% of patients with cirrhosis[4]. Moderate thrombocytopenia and severe thrombocytopenia are observed in approximately 13% and 1%, respectively, of cirrhotic patients, and are dependent upon the stage of cirrhosis. The majority of thrombocytopenia cases are mild to moderate in severity.

Over past decade, there has been significant advances in the understanding of thrombopoiesis, which, in turn, has led to improved understanding of thrombocytopenia in cirrhosis [5]. The characterization of TPO and the results of studies aimed at evaluating TPO pathophysiology in patients with liver disease have revealed a new scenario regarding the possible mechanisms of thrombocytopenia in the course of CLD.

a) Decreased production of platelets :-

- *LowThrombopoietin (TPO)level* – TPO has a significant pathophysiological role. It is produced by the liver at a constant rate and is cleared from circulation upon binding to its receptor (c.Mpl) on both megakaryocytes and platelets. TPO is a glycoprotein consisting of 353 amino acids. Its aminoterminal binds to the c.Mpl receptor and shares remarkable homology with erythropoietin (EPO) while, Carboxy.terminal domain does not affect the activity of the protein in vitro. TPO acts at all levels of megakaryocytopoiesis together with other cytokines. It is the sole regulator of platelet production and steady stateof platelet level [6]. Low TPO serum levels observed in cirrhotic patients are mainly the result of the decreased hepatic production of this hormone.

The megakaryocytopoiesis process.

Serum TPO levels in cirrhotic patients are 'inappropriately low' for the degree of thrombocytopenia that is observed[7]. Further, it has been observed that TPO serum levels in patients with cirrhosis are decreased in parallel with a decrease in the liver functioning mass, and correlate inversely with the patients' Child.Pugh score. Procedures that relieve portal hypertension, such as partial splenic embolization, produce an increase in platelet count that is mainly because of an improvement in liver function and consequently in TPO secretion.

- *Bone Marrow Suppression*- Toxic effects of alcohol and viral-induced thrombocytopathy and bone marrow suppression are well known to cause thrombocytopenia [8]. *Immune-complex mediated destruction*- Among patients with chronic viral liver disease, the presence of immune complex-associated platelet clearance and reticuloendothelial destruction have also been described as inducing thrombocytopenia. Immune complex-coated platelets, and their levels gradually increase as the severity of liver disease increases. Levels of PAIgG were inversely correlated with platelet count.
- *Treatment Induced Thrombocytopenia* - Interferon based antiviral treatment is recommended for chronic hepatitis B virus (HBV) or HCV infection [9]. Interferon causes thrombocytopenia and neutropenia by inhibiting the progenitor cells of all hematological lineages. During interferon-based therapy, the thrombopoietin response is involved in the development of thrombocytopenia[10]. In a study increase in thrombopoietin levels was relatively small for the decrease in platelet count among the patients without cirrhosis (median increase 43 %) and even decreased among cirrhotic patients (median decrease of 5 %).

b) Splenic sequestration:-

- *Hypersplenism and splenic sequestration*- Thrombocytopenia results due to increased pooling of platelet in spleen enlarged by congestive splenomegaly secondary to portal hypertension as a result of cirrhosis. Normally, 20 – 40 % of platelets is pooled in spleen with 1/3rd of their life-span spent in spleen (around 3 days). The percentage is significantly increased in hypersplenism and splenomegaly as a result of cirrhosis.

c) Increased destruction of platelets :-

- *Consumption coagulopathy*- It can be responsible for decrease in platelet count observed in cirrhotic patients with sepsis or shock.
- *Autoantibody mediated destruction of platelets*- Anti-GPIIb–IIIa antibody causes destruction of platelets in cirrhosis patients. The antibody producing B cells in those patients was significantly greater than in the healthy controls (10.9 ± 6.2 vs. 0.4 ± 0.3/105 PBMCs, $p < 0.001$). Even compared with patients with ITP, this frequency was higher among patients with liver cirrhosis (8.2 ± 5.2 for ITP patients, $p = 0.007$). This study suggested that platelet destruction induced by autoantibodies may partly contribute to the occurrence of thrombocytopenia in this specific population, plasma glycocalicin was also assessed. The glycocalicin index, which a is measure of platelet destruction significantly higher among patients with HCV-induced cirrhosis (1.96 ± 1.40), alcoholic cirrhosis (1.79 ± 1.51), or HBV-induced cirrhosis (1.71 ± 1.69) ($p < 0.006$ for all), while it was within normal limits among the healthy subjects (0.9 ± 0.2).

Chronic liver disease is frequently complicated by thrombocytopenia (i.e., platelet count <150 × 109/L), which hampers the medical management of patients . Both prevalence and level of thrombocytopenia are associated with the severity of liver disease, as well as with long-term outcome of the disease.

It can be used as a diagnostic parameter, a prognostic indicator and an epidemiological marker. In clinical practice platelet count alone or in composite scores can be used to identify advanced fibrosis and cirrhosis, which will be helpful in taking decisions which can prevent complication of the disease. It is likely that thrombocytopenia of unknown origin may be an indicator of occult liver disease.

To determine prevalence of thrombocytopenia in CLD patients and correlation of platelet count with child and pugh scores.

MATERIAL AND METHOD

Type of study: Observational study
Study design: Cross sectional study single centre hospital based.
Study population: All patients admitted with CLD in Medicine ward and those attending OPD of N.R.S.M.C.H. , Kolkata.

INCLUSION CRITERIA

1. All patients newly diagnosed with CLD in medicine ward after admission.
2. All patients previously diagnosed with CLD presenting with complications.
3. All patients diagnosed with CLD attending OPD.

EXCLUSION CRITERIA

1. Anyone with infections like dengue
2. Any patient with chronic kidney disease
3. All cases of haematological malignancy
4. Anyone with history of chemotherapy or radiation
5. Patients of malaria or kala azar within three months of completing therapy.
6. Patients on drug like aspirin
7. Cases of aplastic anemia

Period Of Study: One year
Sample Size: 101 (one hundred and one)

Parameters To Be Studied

1) Clinical History And Physical Examination

a) BASELINE CHARACTERISTICS including age, sex, body weight, height.
b) DETAILED HISTORY TAKING including addiction history, drug history, occupation and sexual exposure and physical examination of each and every patient.

2) Investigations

a. Study of complete haemogram, liver function test, Na^+, K^+, urea, Creatinine, HBsAg, Anti-HCV antibody, P-Time/INR.
b. Radiological investigations like USG whole abdomen, Chest X-ray PA view, Magnetic Resonance Cholangio Pancreatography & spleeno-portal Doppler study (where indicated).
c. CHILD PUGH SCORES obtained at the time of presentation.

Study Technique

a. After taking detailed history (about onset, current status along with any bleeding manifestation like hematemesis or rectal, mucosal bleeding any addiction, occupation, history of blood transfusion, exposure or any family history) complete physical examination was done. Higher function was assessed using MMSE score. Examination included assessment of hepato-splenomegaly, presence of ascites by eliciting shifting dullness or fluid thrill. Amount of fluid was assessed by measuring abdominal girth at umbilical level using measuring tape. Other features of portal hypertension was searched for. Evidence of bleeding from any site was thoroughly searched. Grading of encephalopathy was done using West Haven criteria (WHC).
b. Complete haemogram was done to see presence of any thrombocytopenia, anaemia and to rule out any infections.
c. LFT, P-time/INR was done to assess the hepatic function.
d. Patients was then categorized using CHILD PUGH SCORING SYSTEM to see the prognosis. Degree of thrombocytopenia with or without any bleeding manifestation will be assessed for each patient in each category.

Child Pugh Scoring :-

The score employs five clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe derangement.
Chronic liver disease is classified into Child–Pugh class A to C, employing the added score from above.

RESULT AND DISCUSSION

In our study, 4(4.0%) patients were ≤30 years old, 22(21.8%) patients were 31-40 years old, 33(32.7%) patients were 41-50 years old, 20(19.8%) patient were 51-60 years old, 17(16.8%) patient were 61-70 years old, 4(4.0%) patient were 71-80 years old and 1(1.0%) patient were 81-90 years old. In our study, 6(5.9%) patients were Female and 95(94.1%) patient were Male. In our study, 20(19.8%) patients had Present Anemia. In our study, 95(94.1%) patients were Alcoholic, 2(2.0%) patient had Hepatitis B, 1(1.0%) patient had Hepatitis C, 1(1.0%) patient had PBC and 1(1.0%) patient had Wilsons disease. In our study, 29(28.7%) patients had Normal thrombocytopenia, 40(39.6%) atients had Mild thrombocytopenia, 28(27.7%) patients had Moderate hrombocytopenia and 4(4.0%) patients had Severe thrombocytopenia. In our study, 8(7.9%) patients had Mild Ascites, 78(77.2%) patients had Moderate Ascites and 15(14.9%) patients had Severe Ascites. In our study, 9(8.9%) patients had Encephalopathy Grade 1, 12(11.9%) patients had Encephalopathy Grade 2, 5(5.0%) patients had Encephalopathy Grade 3 and 10(9.9%) patients had Encephalopathy Grade 4. In our study, 2(2.0%) patients were in Child Pugh Stage A, 50(49.5%) patients were in Child Pugh Stage B and 49(48.5%) patients were in Child Pugh Stage C. In our study, 1(1.0%) patients had History of UGIB Haematemesis, 7(6.9%) patients had History of UGIB Malena and 4(4.0%) patients had History of Malena & Haematemesis. Association of Age in years vs Thrombocytopenia was not statistically significant (p=0.2944).

Afdhal N et al [11](2008) found that thrombocytopenia (platelet count <150,000/μL) 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/μL–75,000/μL) occurs in approximately 13% of patients with cirrhosis.

Cholongitas E et al [12] (2005) found that prognosis in cirrhotic patients has had a resurgence of interest because of liver transplantation and new therapies for complications of end‐stage cirrhosis. The Model for End‐stage Liver Disease score is now used for allocation in liver transplantation waiting lists, replacing Child‐Turcotte‐Pugh score. Based on current literature, model for end‐stage liver disease score does not perform better than Child‐Turcotte‐Pugh score in non‐transplant settings. Modified Child‐Turcotte‐Pugh and model for end‐stage liver disease scores need further evaluation.

Miller JB et al [13](2019) found that thrombocytopenia is a common complication of chronic liver disease and creates clinical challenges for patients who need invasive procedures.

Sigal SH et al [14](2020) found that thrombocytopenia is a frequent complication in patients with cirrhosis. As many as 84% of patients with cirrhosis have thrombocytopenia, and it is an independent variable indicative of advanced disease and poor prognosis.

Peck‐Radosavljevic M et al [15](2017) found that thrombocytopenia is a common haematological disorder in patients with chronic liver disease. It is multifactorial and severity of liver disease is the most influential factor.

Hancox SH et al [16](2013) found that liver disease is frequently missed as the cause for a patient's thrombocytopenia. All patients with unexplained thrombocytopenia should be evaluated to see if liver disease is present, even when liver function tests are normal.

Giannini EG et al [17](2006) found that in patients with liver disease, thrombocytopenia is a clinical feature that may represent an obstacle to invasive diagnostic or therapeutic procedures, chemotherapy, and anti‐viral treatment. Human studies with thrombopoietin‐mimetic agents are eagerly awaited in order to assess both effectiveness and safety of these drugs.

Saab S et al [18](2020) found that thrombocytopenia is a consequence of portal hypertension and is the most common hematological manifestation of chronic liver disease (CLD) (ie, cirrhosis).

Our study showed that association of History of UGIB (Hematemesis /Malena) vs Thrombocytopenia was not statistically significant (p=0.8318). In Normal Group, the mean Haemoglobin (mean± s.d.) of patients was 8.8690± 2.3501. In Mild Group, the mean Haemoglobin (mean± s.d.) of patients was 8.6225± 1.8363. In Moderate Group, the mean Haemoglobin (mean± s.d.) of patients was 8.7964± 1.7593. In Severe Group, the mean Haemoglobin (mean± s.d.) of patients was 9.0000± 3.0930. Difference of mean Haemoglobin with fourth Group

was not statistically significant (p=0.9535). In Group- A, the mean Platelet count (mean± s.d.) of patients was 193500.0000± 37476.6594. In Group- B, the mean Platelet count (mean± s.d.) of patients was 131340.0000± 41966.2693. In Group- C, the mean Platelet count (mean± s.d.) of patients was 121244.8980± 61566.8778. Difference of mean Platelet count with was not statistically significant (p=0.1323). In Mild Group, the mean Platelet count (mean± s.d.) of patients was 161375.0000± 47919.3892. In Moderate Group, the mean Platelet count (mean± s.d.) of patients was 130294.8718± 50722.8551. In Severe Group, the mean Platelet count (mean± s.d.) of patients was 96066.6667± 54916.1265. Difference of mean Platelet count with was statistically significant (p=0.0112). In above table showed that the mean Age yrs (mean± s.d.) of patients was 50.2772± 12.5157.

SUMMARY AND CONCLUSION

In our study, 20(19.8%) patients had Present Anemia. 29(28.7%) patients had Normal thrombocytopenia, 40(39.6%) patients had Mild thrombocytopenia, 28(27.7%) patients had Moderate thrombocytopenia and 4(4.0%) patients had Severe thrombocytopenia.

In our study, 2(2.0%) patients were in Child Pugh Stage A, 50(49.5%) patients were in Child Pugh Stage B and 49(48.5%) patients were in Child Pugh Stage C.

We found that Etiology was not significantly associated with Thrombocytopenia severity

It was found that in Severe Thrombocytopenia, 2(50.0%) patients had Moderate Ascites and 2(50.0%) patients had Severe Ascites which was statistically significant.

In Severe Thrombocytopenia, 2(50.0%) patients were in Child Pugh Stage B and 2(50.0%) patients were in Child Pugh Stage C. Association of Child Pugh Stage with Thrombocytopenia was statistically significant.

We found that mean Platelet count was low in Severe Thrombocytopenia which was statistically significant.

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