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General Medicine

A STUDY ON HEMATOLOGICAL ABNORMALITIES IN CIRRHOSIS.

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ABSTRACT Cirrhosis of liver is associated with multiple hematological abnormalities, primarily Anemia, Thrombocytopenia, Leucopenia and coagulopathy. These not only add to the morbidity and mortality, but also have clinical implications in the management of these patients. Hence this study was taken up to assess the some of the hematological indices. **Methodology-** 50 patients of Cirrhosis of liver were studied with respect to their bleeding manifestations and their Hemoglobin, platelets counts and Prothrombin time. **Results-** Anemia was found in 82% (n=41) and Thrombocytopenia was found in 72% (n=36) of the patients. 23 patients had an elevated Prothrombin time. 32 patients had upper gastrointestinal varices and 2 of them had variceal bleed, both of whom had severe thrombocytopenia (platelets <50,000.cumm). **Conclusion-** Mean platelet count was significantly lower in the patients with variceal bleed.

KEYWORDS : Cirrhosis, Anemia, Thrombocytopenia, Coagulopathy

INTRODUCTION-

Cirrhosis has been a significant cause of morbidity and mortality worldwide, with a global prevalence of 4.5% to 9.5%. Cirrhosis of liver refers to the late stage of progressive hepatic fibrosis, which is characterized histopathologically by distortion of hepatic architecture with formation of regenerative nodules. This results in consequent reduction in the hepatocellular mass and also disturbs the blood flow within the liver, secondary to the architectural distortion.

Hepatocellular failure by itself, the accompanying complications namely, Portal Hypertension and Splenomegaly and the factors related to the cause of the chronic liver disease lead to abnormal hematological parameters in Cirrhotic patients. These hematological abnormalities primarily consist of anemia due to various pathomechanisms, thrombocytopenia and coagulopathy. These significantly add to the morbidity and mortality in a vast majority of them. The etiology behind these abnormalities is multifactorial and are described below.

PATHOGENESIS-

1) Portal hypertension- The loss of architecture within the liver causes resistance to the portal blood flow, consequently leading to Portal Hypertension. More than 60% of patients with Cirrhosis have clinically significant Portal hypertension. A key feature of Cirrhotic Portal Hypertension is Splenomegaly. This enlarged spleen sequesters and further prematurely lyses a massive number of formed elements of the blood/blood cells (Red blood cells, white blood cells and platelets). This is termed as Hypersplenism. According to studies, approximately up to 90% of the platelet reserve has been shown to be sequestrated within the enlarged spleen in cirrhosis. (1-3) This causes Thrombocytopenia, which is one of the earliest features of portal hypertension. Subiyah and Al-Hindawi demonstrated in vivo accumulation of ^{51}Cr-labelled red cells in cases of cirrhosis of liver with splenomegaly and thus correlated between reduced red cell survival and splenomegaly in cirrhosis. (4)

2) Nutritional deficiencies- due to poor nutritional intake and reduced appetite, poor absorption due to gastric and intestinal portal venous congestion and increased losses. In addition, Chronic alcoholism also impairs absorption, metabolism and utilization of Thiamine, folic acid, Vitamin B12, zinc and other vitamins and trace elements.

3) Direct toxic effect of alcohol on the bone marrow - Chronic excessive alcohol consumption depletes the number of hematopoietic precursor cells in the bone marrow and brings about distinctive structural abnormalities in these cells, leading to a contracted pool of or nonfunctional mature blood cells. This causes moderate anemia; decreased number of leucocytes, especially of neutrophils; and moderate to severe thrombocytopenia. This generalized decrease in the blood cell counts (i.e., pancytopenia) is very uncommonly progressive or fatal and is often correctable with abstinence from alcohol. (5)

4) Thrombopoietin is a cytokine which is required for the production of megakaryocytes and platelets. It is predominantly produced in the liver, but also to some extent in the bone marrow and the kidneys. Studies have shown that patients with Cirrhosis lower circulating levels of this cytokine, probably because of reduced synthesis or release by the hepatocytes and also that there may be reduced response to this cytokine in these patients. (6,7)

5) Bone marrow suppression due to Viral hepatitis B, C can cause pancytopenia. (8)

6) Hemolysis-
i) Spur cell anaemia – seen in advanced chronic liver disease, more-so in alcoholics. It is called Zieve's syndrome and results from the disruption the red cell-membrane due to the effects of hyperlipidemia and abnormal lipids.(17)
ii) Around 10% of patients who are a combination of interferon and ribavirin therapy (for Hepatitis C) can have significant dose-dependent hemolytic anaemia. (18)
iv) Autoimmune hepatitis can be associated with autoimmune hemolytic anaemia.

7) Autoantibodies to platelets - presenting like idiopathic thrombocytopenic purpura (ITP), often seen in HCV infection.

8) Abnormalities in coagulation- As chronic liver disease progresses, it causes a decrease in the levels of procoagulant factors, with the exception of factors such as factor VIII and von Willebrand factor, which are increased.

But this is associated with a fall in the levels of anticoagulants such as antithrombin and protein C, since these are also produced by the liver. Thus in Chronic liver disease, there is a decrease in anticoagulant proteins which balances out to certain extent, the decrease in procoagulants, so as to produce a new state of balance/homeostasis, termed by some as "Rebalanced hemeostasis". (9-11) These changes in the clotting function are reflected in the Prothrombin time and Partial thromboplastin time. Studies have shown a correlation between the degree of derangement in PT and the severity of hepatocellular failure. It is also constant parameter in the Child–Pugh (CP) score and model for end-stage liver disease (MELD) scoring systems, which are used for prognostication.

The presence of thrombocytopenia, leucopenia, anemia, coagulopathy in cirrhotics has major clinical repercussions. When these patients require invasive procedures such as liver biopsy, paracentesis, endoscopic or surgical procedures, these hematological abnormalities severely restrict the scope of carrying out these procedures due to fear of hemorrhagic complications. Chronic anemia can add to a poorer outcome post bleeding complications. Hence this study was taken up in view of the clinical implications.

AIMS OF THE STUDY

1) To assess the percentage and severity of anemia in patients with Cirrhosis.
2) To assess the percentage and severity of thrombocytopenia in patients with Cirrhosis.
3) To correlate Prothrombin time elevation and Platelet counts with bleeding manifestations in Cirrhosis.

MATERIALS AND METHODS-

This Observational study was done at Rajarajeswari Medical College and Hospital, Bangalore, during the period from April 2019 to September 2019, after obtaining permission from the institutional ethical committee. 50 patients of Cirrhosis meeting the inclusion and exclusion criteria were selected for this study from among the patients attending the out-patient department and those admitted in the hospital, after obtaining their consent.

Inclusion criteria-

Patients with Cirrhosis of liver, of alcoholic, post infective and metabolic etiology, between the age of 30-70 years.

Exclusion criteria-

1)Patients with primary hematological abnormalities.
2)Patients in sepsis.
3)Patients with acute liver failure.
4)Patients with CKD.
5)Known patients of any malignancy.

All patients were interrogated about their history, examination was done. Then patients were subjected to various investigations. The diagnosis of Cirrhosis was established with Ultrasound, CT abdomen, along with evidence of Upper GI varices/portal hypertensive gastropathy, supported by signs of liver cell failure wherever present. After this, these patients were evaluated for their hematological abnormalities.

Parameters measured were Hemoglobin, MCV, MCH, MCHC, RBC count, Peripheral smear, Retic count, Total leucocyte count, Differential leucocyte count, Platelet count, PT.

Statistical analysis:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. (12-14)

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. Statistical software: SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS-

Of the 50 patients, 46 (92%) were males and only 4 (8%) were females. A majority of our patients belonged to the middle age and the elderly. The mean age was 52.08 ± 9.21 years. Among the 50 patients of Cirrhosis, 39 of them were attributed to Alcoholic liver disease, 6 of them to Chronic Hepatitis B, 1 had Chronic Hepatitis C, 3 of them were attributed to NASH, 1 was cryptogenic.

41 (82%) out of the 50 patients had Anemia. 37 out of 46 males were Anemics. All the 4 females had Anemia. The mean Hb was 10.06 ± 2.56 g/dL.

The distribution of the severity of Anemia among the patients was as follows.

Table 1- Distribution of severity of Anemia.

Grade of Anemia	No. of patients	Percentage
Mild (males 11-12.9 g/dL, Females 11-11.9 g/dL)	6	14.63%
Moderate (8-10.9 g/dL)	24	58.53%
Severe (<8 g/dL)	11	26.82%
Total	41	100%

36 (72%) out of the 50 Cirrhotics had Thrombocytopenia. 2 patients had severe thrombocytopenia (<50,000 cells/cumm). 11 patients had platelets between 50,000-1 lac cells/cum and 23 of them had between 1 to 1.5 lacs. The mean platelet count was 1,27,800.00 ± 45125.67 cells/cumm.

Upper GI varices on Endoscopy- 32 out of the 50 patients had Upper GI varices on Endoscopy. The only bleeding manifestation the patients had was Variceal bleeding. Only 2 out of the 32 patients with varices had presented with of a recent variceal bleeding.

Prothrombin time (PT) was elevated in 23 out of the 50 patients. (Normal reference range at our laboratory- 12-18 seconds). Mean PT was 17.79 ± 3.89 seconds 11 of the 32 patients with varices has an elevated PT. Only 1 of the 2 patients with variceal bleed was found to have an elevated PT value. But there was no statistically significant association with the PT values. ($\chi 2 = 0.2309$, df =1, p = 0.6309)

Table 2- Platelet counts compared against the variceal bleed.

Platelet count (cells/cumm)		Variceal bleed			
		Yes		No	
		Count	%	Count	%
PC	<50,000	2	100.0%	0	0.0%
	50,000 to 1 lac	0	0.0%	11	36.7%
	1 lac to 1.5 lacs	0	0.0%	13	43.3%
	1.5 to 2 lacs	0	0.0%	5	16.7%
	>2 lacs	0	0.0%	1	3.3%

$\chi 2 = 32$, df =4, p <0.001* (Significant)

The platelet counts in the patients with varices, with and without variceal bleeding is as above. Mean platelet count was significantly lower among subjects with Variceal bleed.

Table 3- Table showing Mean age, Hb, Platelet count and Prothrombin time with respect to Variceal bleed among subjects with Varices.

	Variceal bleed						P value
	Yes		No		Total		
	Mean	SD	Mean	SD	Mean	SD	
Age	47.00	1.41	54.87	7.77	54.38	7.77	0.169
Hb	8.10	1.41	9.48	2.69	9.39	2.63	0.482
Platelets	41000.00	1414.21	114900.00	39799.80	110281.25	42570.04	**0.015***
PT (sec)	20.50	4.81	16.88	3.65	17.11	3.74	0.190

The mean platelet count was significantly lower among subjects with Variceal bleed. The difference between the mean values of PT is not significant.

DISCUSSION

In the present study, 50 patients of Cirrhosis were studied taking into account their haematological parameters namely Hemoglobin concentration, Platelet count and prothrombin time.

Of the 50 patients, 46 (92%) were males and only 4 (8%) were females. The mean age was 52.08 ± 9.21 years.

Among the 50 patients of Cirrhosis, 39 of them were attributed to Alcoholic liver disease, 6 of them to Chronic Hepatitis B, 1 had Chronic Hepatitis C, 3 of them were attributed to NASH, 1 was cryptogenic.

41 (82%) out of the 50 patients had anemia of some degree. The percentage of anemics among the patients with Cirrhosis is higher compared to previous studies. The mean Hb was 10.06 ± 2.56 g/dL.

36 (72%) out of the 50 Cirrhotics had Thrombocytopenia. The mean platelet count was 1,27,800.00 ± 45125.67 cells/cumm. The percentage of Cirrhotic patients with Thrombocytopenia correlated with previous studies.

Study done by Qamar AA, Grace ND et al on 213 patients with Cirrhosis found that 21.1% of their subjects had anemia and 77.9% had Thrombocytopenia. (15)

Upper GI varices on Endoscopy- 32 out of the 50 patients had Upper GI varices on Endoscopy. The only bleeding manifestation the patients had was Variceal bleeding. Only 2 out of the 32 patients with varices had presented with of a recent variceal bleeding.

Prothrombin time (PT) was found to be elevated in 23 (46%) out of the 50 patients. 11 of the 32 patients with varices has an elevated PT. Only 1 of the 2 patients with variceal bleed was found to have an elevated Prothrombin Time value. But there was no statistically significant association with the PT values. This finding was similar to the study conducted by Pahwa AR, Dudani S. et al. (16) This finding could have been because of the small sample size out of which only 2 patients had an upper gastrointestinal (GI) bleed.

Out of the 32 patients with Varices, 26 of them had thrombocytopenia. 2 of them has a platelet count of less than 50,000 cells/cumm, who also had an upper GI bleed. The Mean platelet count was found to be significantly lower among subjects with Variceal bleed.

CONCLUSION-

Our study showed a statistical significant lower mean platelet count among the patients with variceal bleed. But further studies need to be taken up which study regarding the bleeding manifestations in detail also with respect to the grade of varices.

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