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A Study on Management of Comorbidity and Complications In Liver Cirrhosis Patients

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Abstract
Objectives: The main objective is to study on management of comorbidity and complications in liver cirrhosis patients, to study the severity of liver cirrhosis at the time of admission and to identify the risk factors and complications of liver cirrhosis in various populations.
Methods: A prospective observational study has been done in limited period of 1 year in inpatient department of gastroenterology and general medicine. We have excluded the patients who are non-cooperative and receiving less than 24hrs of emergency care. We have included the patients who are admitted in inpatient department of gastroenterology and general medicine and the cases with demographic details and with or without social habits.
Results and Conclusion: In this study we found that male patients were 91out of 122 cases and were more prone to liver disease as alcohol is the main risk factor where alcoholic patients were 79 out 122 cases with 64.75%.The Pantoprazole PDD was 47.5 and ratio between PDD:DDD (47.5:40) was 1.1, Octreotide PDD was 0.171 and ratio between PDD:DDD (0.171:0.7) was 0.244, Ciprofloxacin PDD was 1000mg and ratio between PDD:DDD (1000:1000) was 1, Furosemide PDD was 49.33 and the ratio between PDD:DDD (49.33:40) was 1.23, PropanololPDD was 39.41 and the ratio between PDD:DDD (39.41:160) was 0.24, Metoclopramide PDD was 20.12 and the ratio between PDD:DDD (20.12:30) was 0.66, Ketorolac PDD was 60 and the ratio between PDD:DDD (60:30) was 2, Tramadol PDD was 32.57 and the ratio between PDD:DDD (328.57:300) was 1.09, Lactulose PDD was 523.5 and the ratio between PDD:DDD (523.5:670) was 0.78, Ranitidine PDD was 130 and the ratio between PDD:DDD (130:300) was 0.43, Hyoscinebutylbromide PDD was 96 and the ratio between PDD:DDD (96:100) was 0.96. The main complications in liver cirrhosis was found to be portal hypertension 35.94% and ascites 20.2% out of 122 cases.
Conclusion: The complications of liver cirrhosis like portal hypertension and ascites are more common than other complications. Risk factors were common in males than females as alcohol is the established risk factor.

Key Words: Liver cirrhosis, Portal hypertension, Ascites, Prescribing Daily Dose(PDD), Defined Daily Dose(DDD)

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I. INTRODUCTION

The word cirrhosis comes from the Greek word kirrhos which means orange yellow[1]. Laennec gave cirrhosis its name kirrhos in 1819 in a brief footnote to his treatise De I 'auscultation mediate[2].The definition of cirrhosis remains morphological, described by a working party for the World Health Organization(WHO) in 1978 as "a diffuse process characterized by fibrosis and the conversion of normal liver architectures structurally abnormal nodules[3]. Cirrhosis is the chronic disease of the liver in which diffuse destruction and regeneration of hepatic parenchymal cells has occurred, in which diffuse increase in connective tissue has resulted in disorganization of the lobular architecture. The triad of parenchymal necrosis, regeneration and scarring is always present regardless of individual clinical manifestations [4]. Certain reversible components of cirrhosis have been indicated where significant histological improvement have occurred with regression of cirrhosis but complete resolution with a return to normal architecture seems unlikely [5]. The underlying immunological response has usually been acting for months or years where inflammation and tissue repairing are in progress simultaneously which leads in the end to fibrosis and cirrhosis [6]. The main causes of cirrhosis are alcoholic liver disease(ALD),hepatitis B(HBV), hepatitis C(HCV),non-alcoholic steatohepatitis, haemochromatosis, autoimmune hepatitis, primary biliary cirrhosis(PBC) and primary sclerosing cholangitis(PSC) [7]. The natural history of cirrhosis can be divided into a preclinical and a subsequent clinical phase. The preclinical phase is usually prolonged over several years once clinical events occur such as ascites,encephalopathy,variceal bleeding

or the development of hepatocellular carcinoma the remaining course of the disease is much shorter and usually fatal [8]. The complications of liver cirrhosis are Ascites is the pathologic accumulation of lymph fluid within the peritoneal cavity. Portal hypertension is increase in the blood pressure within a system of veins valled the portal venous system. Oesophagealvarices is the abnormal veins in the lower part of the tube running from the throat to the stomach. Hepatic encephalopathy is the spectrum of neuropsychiatric abnormalities in patients with liver dysfunction. Bacterial peritonitis is the infection of ascitic fluid that occurs without warning cause and the hepatorenal syndrome are the complications in liver cirrhosis [9]. The etiologies for liver disease in pediatric population are many however they can be classified broadly into infections, immunologic, metabolic toxin or drug related indeterminate and diseases [10] Worldwide death rates from alcohol related liver cirrhosis has been decreasing but an increase has been observed in a few Eastern countries and England [11]. The exact prevalence of cirrhosis is unknown. Cirrhosis is responsible for more than 26000 deaths and ranked 12th among leading cause of death and is responsible for 1.2% of all U.S deaths. In the United States there has been an increase in the proportion of patients with HCV compared to ALD in the recent years [12]. In internationally 14^{th} most common cause of death but in Europe 4^{th} most common cause of death. In India according to WHO data published 2015 liver deaths are 2.44% of total deaths. Chronic alcohol consumption and Chronic viral hepatitis (type B, C&D) are most common causes in cirrhosis of liver but anything that damages the liver can cause cirrhosis including:1) Metabolic liver disease: Hemochromatosis, Wilsons disease, Fatty liver 2) Cholestatic liver disease: Primary biliary cirrhosis, Secondary biliary cirrhosis, Budd Chiari syndrome 3)Drugs and Herbals: Isoniazid, Methyldopa, Phenothiazine, Jamaica bush tea, Amiodarone. The management of ascites include diet, diuretics, paracentesis, Trans jugular intrahepatic portosystemic shunt[13, 14]. The management of spontaneous bacterial peritonitis include prophylaxis if undergoing paracentesis, antibiotic therapy. The management of portal hypertension unfortunately most causes cannot be treated. Instead treatment focusses on managing the complications are diet, non-selective beta blockers, endoscopic therapy, surgery and radiology procedures have role in preventing the complications.The management of variceal bleeding include vasoactive drug therapy, volume resuscitation, sclerotherapy, pharmacologic prophylaxis. The management of hepatic encephalopathy include ammonia reduction, elimination of drugs causing CNS depression, limit excess protein in diet. The management of hepatorenal syndrome include NSAIDS, decrease diuretics, volume resuscitation, and liver transplantation. The management of hepatopulmonary syndrome include paracentesis and oxygen therapy. The monitoring parameters is based on management approach of liver cirrhosis. The monitoring parameters of ascites is daily assessment of weight. The monitoring parameters of spontaneous bacterial peritonitis is evidence if clinical deterioration (abdominal pain, fever, anorexia, fatigue). The monitoring parameters of variceal bleeding is Child Pugh score, endoscopy, and complete blood count. The monitoring parameters of coagulation disorder is complete blood count, prothrombin test, platelet count. The monitoring parameter of hepatic encephalopathy is psychological testing, concurrent drug therapy, EEG, mental status changes. The monitoring parameters of hepatorenal syndrome is serum and urine electrolytes, concurrent drug therapy. The monitoring parameters of hepatopulmonary syndrome isdyspnoea and presence of ascites. The aim of this is identify the various risk factors and complications of liver cirrhosis in various populations (Like Pediatric, Adult, Geriatric) and calculate the Prescribed Daily Dose and calculate the ratio between the Prescribed Daily Dose (PDD) and Defined Daily Dose (DDD)

II. METHODOLOGY

This is a prospective observational study conducted over a period of one year (March 2016-March 2017). All the patients those are admitted in hospital reviewed on daily basis. Those are reached my inclusion criteria patients who are admitted in general medicine with liver cirrhosis and both sex of all age group. We have excluded patients who are non-co-operative and patients receiving less than 24hrs of emergency care. A totalof 122 patients enrolled into the study and collected all necessary information like demographic details, laboratory reports, treatment charts and past medication history by interviewing patient care takers. All the patients will be monitored from day of admission until discharge from the wards. Patient case notes, medication charts, laboratory findings and other relevant data were reviewed. All the information was collected in well-designed data collection form. We calculated PDD and expressed them as the PDD : DDD ratio. The defined daily doses for the defined daily doses for the selected 12 class of drugs were taken from pre-calculated DDD from WHO. The calculated PDD of the drugs are compared with DDD by using simple-t test. All the collected data was entered into MS-Excel. The raw data was taken into SAS software by using Proc Import and data was redesigned/reorganised with number and character function and PDD was calculated by using proc means and compared PDD with DDD by using Proc t-test (simple t-test).

III. RESULTS:

During the study period (August 2016-january 20017) total 900 patients were reviewed among them 122(13.55%) enrolled into the study according to inclusion criteria, the remaining 778(86.44%) patients were excluded based on the exclusion criteria. The 122 male and female patients are distributed according to rural and urban areas its shows in **Table: 1**

Table 1: Patients distributed according to sex and area.

Sex	**Area N (%)**		**P value**
	Rural	**Urban**	
Male	39 (31.97)	52 (42.66)	0.68
Female	12 (9.84)	19 (15.57)	

In 122 patients 91(74.59%) are male and 31(25.41) are female and the ratio between male and female is 3:1. In our study 41.8% was from urban areas while 58.2% was from rural areas. A most of the rural area people were unaware of the illness, most of the cases were admitted in severe conditions.

In 122 patients 84 (68.85%) were found to be smokers and 79 (64.75%) were found to be alcoholic which indicates smokers and alcoholics are at high risk. However in non-alcoholic patients were found to be admitted with obesity and geriatric patients. In this people with both smoking and non-alcoholic are not observed details were given **Table: 2**.

Table 2: Patients distributed according to Smoker and Alcoholic

Smoking	**Alcoholic N (%)**		**P value**
	No	**Yes**	
Yes	43 (35.25)	41 (33.61)	<0.0001
No	0 0.0	38 (31.15)	

Majority of the cases i.e., about 81.7% were confirmed with chronic liver disease and abscess 9.84%, jaundice 4.92% and others 3.25% details were given **Table: 3**.

Table 3: Patients distributed according to diagnosis.

SNO	**Diagnosis**	**No. of patients**	**Percent**
1	Abscess	12	9.84
2	Chronic liver disease	100	81.97
3	Jaundice	6	4.92
4	Others	4	3.25

Among the patients enrolled with liver cirrhosis 35.9% of patients were developed with portal hypertension which is higher than other complications, followed by Ascites 20.2%, Esophageal varices 16.9%, Hepatic encephalopathy 5.8%, Bacterial peritonitis 1.96%, Jaundice 10.4%, Others 9% are the complications seen in 122 patients. Details were given **Table: 4**

Table 4: **Patients distributed in accordance with their complications.**

Sl.NO	**Complications**	**Frequency**	**Percent**
1	Portal Hypertension	55	35.94
2	Esophageal varices	26	16.9
3	Ascites	31	20.2
4	Hepatic Encephalopathy	9	5.8
5	Bacterial peritonitis	3	1.96
6	Jaundice	16	10.4
7	Others	17	9

Prescribed daily dose was collected from 122 cases of prescription and related with diagnosis on which the dosage is based. In 122 cases 12 classification of drugs were used. As noted the main purpose of DDD is a tool for improving the drug use.

In Liver Cirrhosis patients commonly prescribed medication was Proton pump inhibitors, Somatostatin analogue, Antibiotics, Diuretics, Beta blockers, Anti emetics , Non-steroidal anti-inflammatory drugs, Opioid analgesic, Hepatic protector, Laxative, H2 receptor blocker, Antispasmodics. PDD of all the drug used in liver cirrhosis was given in **Table: 5**

Table 5: Comparison of PDD and DDD

S.NO	Classification	Drug	PDD(mg)	DDD(mg)	PDD:DDD
01	Proton pump inhibitor	Pantoprazole	47.58	40	1.18
02	Somatostatin Analogue	Octreotide	0.17142	0.7	0.244
03	Antibiotics	Ceftriaxone	2062.2	2000	1.03
		Ciprofloxacin	1000	1000	1
		Metronidazole	912.90	500	1.82
		Doxycycline	107.14	100	1.07
		Piperacillin	320.83	14000	0.02
		Rifaximin	1251.06	600	2.08
04	Diuretics	Furosemide	49.33	40	1.23
		Spiranolactone	48.57	75	0.65
05	Beta blockers	Propanolol	39.41	160	0.24
06	Anti-emetics	Metoclopramide	20.12	30	0.66
		Ondansetron	7.88	16	0.49
07	NSAIDS	Ketorolac	60	30	2
		Paracetamol	990.90	3000	0.33
08	Opioid Analgesic	Tramadol	328.57	300	1.09
09	Hepatic Protector	Ursodeoxycholic acid	654.05	750	0.87
10	Laxative	Lactulose	523.5	670	0.78
11	H_2 Receptor Blocker	Ranitidine	130	300	0.43
12	Anti Spasmodics	HyoscineButylbromide	96	100	0.96

In Proton pump inhibitors, Pantoprazole was prescribed in almost all the cases and PDD was 47.58mg and the ratio between PDD: DDD (47.58: 40) was 1.18. The pantoprazole PDD was nearly same as DDD. In Somatostatin analogue, Octreotide was prescribed and PDD was 0.17mg and the ratio between PDD: DDD (0.17:0.7) was 0.244. In Antibiotics, Ceftriaxone was prescribed and PDD was 2062.2mg and the ratio between PDD:DDD (2062.2 : 2000) was 1.03, Ciprofloxacin PDD was 1000mg and ratio between PDD:DDD (1000:1000) was 1, Metronidazole PDD was 912.90mg and the ratio between PDD:DDD (912.90:500) was 1.82, Doxycycline PDD was 107.14mg and the ratio between PDD:DDD(107.14:100) was 1.07, Piperacillin PDD was 320.83mg and the ratio between PDD:DDD (320.83::14000) was 0.02, Rifaximin PDD was 1251.06mg and the ratio between PDD:DDD (1251.06:600) was 2.08.In Diuretics, Furosemide was prescribed and PDD was 49.33mg and the ratio between PDD: DDD (49.33:40) was 1.23, Spiranolactone PDD was 48.57mg and the ratio between PDD: DDD (48.57:75) was 0.65.In Beta blockers, Propanolol was prescribed and PDD was 39.41mg and the ratio between PDD: DDD (39.41:160) was 0.24. In Anti-emetics, metoclopramide was prescribed and PDD was 20.12mg and the ratio between PDD: DDD (20.12:30) was 0.66, Ondansetron PDD was 7.88mg and the ratio between PDD: DDD (7.88:16) was 0.49. In Non-steroidal anti-inflammatory drugs, Ketorolac was prescribed and PDD was 60mg and the ratio between PDD:DDD (60:30) was 2, Paracetamol PDD was 990.9mg and the ratio between PDD:DDD (990.0:3000) was 0.33.In Opioid Analgesic, Tramadol was prescribed and PDD was 328.57mg and the ratio between PDD: DDD (328.57:300) was 1 H2 Receptor Blocker, Ranitidine was prescribed and PDD was 130mg and the ratio between PDD: DDD (130:300) was 0.43.In Anti Spasmodics, HyoscineButylbromide was prescribed and PDD was 96mg and the ratio between PDD: DDD (96:100) was 0.96..09. In Hepatic protector, Ursodeoxycholic acid was prescribed and PDD was 654.05mg and the ratio between PDD: DDD (654.05:750) was 0.87.In Laxative, Lactulose was prescribed and PDD was 523.5mg and the ratio between PDD: DDD (523.5:670) was 0.78 In Anti Spasmodics, HyoscineButylbromide was prescribed and PDD was 96mg and the ratio between PDD:DDD (96:100) was 0.96.

IV. DISCUSSION

During the study period (March 2016-March 2017) total 900 patients were reviewed among them 122 (13.55%) enrolled into the study according to the inclusion criteria the remaining 778 (86.44%) patients were excluded based on the exclusion criteria. In 122 patients men were 74.5% and female were 25.5% and the ratio

between male and female were 3:1. Male population was more prone to liver cirrhosis when compared to women in India as alcohol is the established risk factor for Liver cirrhosis. 41.8% of the population in our study was from urban areas while 58.2% was from rural areas. In another study done by NamrataA Desai et al 2015, was found to be 78% were male and 22% were female, urban population was found to be more susceptible to liver diseases [15]. In 122 patients 68.85% i.e.84 patients were found to be smokers and 64.75% i.e.79 patients were found to be alcoholic which indicates smokers and alcoholics are at more risk. However in non-alcoholics patients were found to be admitted with obesity and geriatric patients. Among the patients enrolled with liver cirrhosis, 35.9% of patients were developed with portal hypertension which is much higher percent than other complications, followed by ascites with 20.2% ,jaundice with 10.4%, Esophageal varices 16.9%, Hepatic encephalopathy 6%, Bacterial peritonitis 2% and others 11% are the complications seen in 122 patients.
In 122 cases collected 12 classification of drugs were used. Prescribed daily dose was collected from 122 cases of prescription and related with diagnosis on which the dosage is based.

As bacterial infections were very common in advanced cirrhosis in most of the chronic liver disease were prescribed with antibiotics. The PDD and DDD was found to be same in ceftriaxone, ciprofloxacin, doxycycline and doubled in metronidazole and rifaximin. As ascites was the second most common complication in the diagnosis, the aim is to revert the sodium retention and diuretics were used. PDD was more in furosemide than DDD and less in spironolactone with ratio of 1.23 and 0.65 respectively. Beta-blockers were used to lower the blood pressure in varices that bypass the liver and to reduce the risk of bleeding. The PDD was found to be four times less than the DDD with the ratio of 0.24. As noted above the main purpose of ATD/DDD system is a tool for improving the drug use.

V. CONCLUSION

We observed that male was more prone to liver disease than female as the main established risk factor is alcohol. The adult age group was mostly admitted than geriatric patients. Alcoholic patients were more compared to non-alcoholic patients. Rural patients were unaware of their illness and found to be admitted with severe conditions and with progression of the disease when compared to the urban patients. Among the patients diagnosed with liver cirrhosis about 80% of cases were found with chronic liver disease. The complications like ascites and portal hypertension are more common than other complications. With the treatment provided most of the cases have shown a better progress in accordance with Prescribed Daily Dose (PDD) and Daily Defined Dose (DDD) and its ratios.

Study Limitation

Study is conducted in single hospital within limited period of time.

Conflicts of Interest

No conflicts of interest were raised by the authors

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