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Research Article

Study of Propranolol in Cirrhosis Patients with Portal Hypertension: Research at Sidoarjo General Hospital

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Abstract.
Cirrhosis is the final stage of chronic liver disease caused by fibrosis which decreases the function and changes the shape and structure of the liver. Portal hypertension is an essential pathophysiology of cirrhosis, which can lead to an increased risk of death in patients resulting in very detrimental complications originating from portal obstruction of blood flow, such as cirrhosis or blockage of blood vessels. According to the EASL guidelines, non-selective β-blocker therapy such as propranolol can reduce portal pressure by reducing the portal venous flow through two mechanisms: decreased cardiac output and decreased splanchnic blood flow. This study aimed to determine the pattern of using propranolol in patients with liver cirrhosis in Sidoarjo Hospital. This was an observational study with a retrospective approach in cirrhosis patients with portal hypertension from 1st January 2021 until 31st December 2021. The Patient Medication Records (PMR) data was obtained from 15 male patients (68%), with the most age ranging from 56 to 65 years old (37%). The pattern of using single therapy was in 22 patients (100%). The highest use of single treatment was Propranolol (3x10 mg) with 12 patients (52%), Propranolol (2x10 mg) with ten patients (43%), and Propranolol (2x40 mg) with only one patient (5%). Interm of switching therapy, only one medication which is Propranolol (2x10 mg switch toPropranolol (2x40 mg).

Keywords: Propranolol, Portal Hypertention, Cirrhosis

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1. INTRODUCTION

Cirrhosis is a liver injury characterized by fibrosis and a change in the normal structure of the liver into an abnormal structure of nodules. Chronic liver injury causes damage to normal liver tissue resulting in the development of regenerative nodules. Various disorders can injure the liver, including viral infections, toxins, hereditary conditions, or autoimmune processes (1). Cirrhosis is the 11th most common cause of death globally. In the United States, cirrhosis is the 12th leading cause of death (2). Based on data from

the Global Burden of Disease study, the incidence rate of cirrhosis was 20.7 per 100,000 in 2015, it invreased 13% since 2000 (3). Based on the 2016 World Health Organization (WHO) report, the mortality rate for cirrhosis in Indonesia both in male and female was 51.1 and 27.1 per 100,000 population, respectively.

The liver plays an important role in the synthesis of proteins such as albumin, clotting factors, complement factors and the detoxification and storage of vitamin A. In cirrhosis, the development of scar tissue replaces the normal parenchyma and blocks portal blood flow to the organs and affects normal function. Research shows the important role of stellate cells in the development of cirrhosis which generally stores vitamin A. Damage to the liver parenchyma due to inflammation, activates stellate cells and increases fibrosis and inhibits circulating blood flow. Chronic injury to the liver causes inflammation, necrosis and subsequent fibrosis. As of, fibrosis that continues will end up as cirrhosis (4).

The clinical manifestations of cirrhosis are enlargement of the liver beyond its normal size (hepatomegaly), enlargement of the spleen (splenomegaly), ascites, edema, pleural effusion, difficulty breathing, weight loss, and encephalopathy (1). Complications of liver cirrhosis include portal hypertension, ascites, spontaneous bacterial peritonitis (SBP), esophageal variceal bleeding, hepatorenal syndrome, hepatic encephalopathy, and liver cancer(5).

Portal hypertension is a complication of liver cirrhosis which can lead to an increased risk of death (6). Nearly 90% of cirrhotic patients eventually develop portal hypertension and this condition is the origin of most deaths in cirrhotic patients (7). In portal hypertension there is an increasing pressure in the portal system of more than 12 mmHg. Whereas normal portal pressure is between 5-10 mmHg. This situation will cause an enlarged spleen (splenomegaly), dilation of blood vessels in the abdominal wall around the navel (caput medusae), hemorrhoids, and suppression of the esophageal or cardia veins (varices oesophagus) which can cause hematemesis, even melena (8). Management of Portal Hypertension according to EASL guidelines, propanolol nonselective β-bloker (NSBB) become the mainstay for chronic portal hypertension therapy because can reduce heart rate by 25% causing a sustained decrease in portal venous pressure in cirrhotic patients with portal hypertension. In addition, propranolol can prevent variceal bleeding (9).

2. MATERIAL AND METHODS

This research is observational study without give treatment to the sample. Data was collected retrospectively, with a descriptive research design. This descriptive study was used to describe the pattern of propranolol usage in portal hypertension patients because it was carried out by processing Patient Medication Records (PMR) data in cirrhosis patients during January 1 - December 31, 2021.

3. RESULTS

Based on the results of research on cirrhosis patients with portal hypertension who received propranolol at the sidoarjo general hospital inpatient during January 1 to December 31, 2021. We were obtained 22 PMR (Patient Medication Records).

3.1. Patient Demographic Data

TABLE 1: Gender of Cirrhosis Patients with Portal Hypertension.

No.	Gender	N	Percentage (%)
1.	Male	15	68
2.	Female	7	32
	Total	**22**	**100%**

TABLE 2: Age of Cirrhosis Patients with Portal Hypertension.

NO.	Age (y.o)	N	Percentage (%)
1.	36 - 45	4	18
2.	46 - 55	7	32
3.	56 - 65	8	37
4.	>65	3	13
	Total	**22**	**100**

*(Ministry of Health RI, 2009)

TABLE 3: Health Insurance of Cirrhosis Patients with Portal Hypertension.

No.	Health Insirance	N	Percentage (%)
1.	Private	0	0
2.	National (JKN)	22	100
	Total	**22**	**100**

3.2. Complications of Cirrhosis Patients with Portal Hypertension

Table 4: Another Diagnosis .

NO.	Komplikasi	N	Percentage (%)
1.	Acites	6	11
2.	Hematemesis Melena	12	22
3.	Anemia	13	24
4.	Hypoalbumin	1	2
5.	Hepatic encephalopathy	12	22
6.	Diabetes Mellitus	3	6
7.	Hepatitis B	3	6
8.	SBP	4	7
	Total	54	100

*Note: 1 patient can have more than 1 complication

3.3. Pattern of Propranolol Use in Cirrhosis Patients with Portal Hypertension

Table 5: Pattern of Therapy Use in Cirrhosis Patients with Portal Hyppertension.

Therapy	N	Percentage (%)
Single	22	100
Total	**22**	**100**

Table 6: Pattern of Propanolol Single Therapy.

Obat	Dosage/Route	N	Percentage (%)
Propranolol	(2x10 mg) po	10	43
	(3x10 mg) po	12	52
	(2x40 mg) po	1	5
Total		**23**	**100**

Note : *1 patient can get more than one usage pattern

Table 7: Pattern of Propanolol Switching Therapy.

Pola 1	Pola 2	N	Percentage (%)
Propranolol (2x10 mg) po	Propranolol (2x40 mg) po	1	100
Total		**1**	**100**

Table 8: Length Use of Propranolol Therapy.

Duration (days)	N	Percentage (%)
< 3	13	59
3 – 7	8	36
8 – 12	1	5
Total	**22**	**100**

3.4. Length of Hospitalization of Cirrhosis Patients with Portal Hypertension

Table 9: Length of Stay Cirrhosis Patients with Portal Hypertension.

Length (days)	N	Percentage (%)
< 3	2	9
4 – 10	18	82
> 11	2	9
Total	**22**	**100**

3.5. Discharged Conditionfrom Hospital of Cirrhosis Patients with Portal Hypertension

Table 10: Discharged Condition of Chirrosis Patients Portal Hypertension.

Condition	N	Percentage (%)
Getting Better	22	100
Total	**22**	**100**

4. DISCUSSION

Based on **Table 1.1** shows the incidence of cirrhosis is more suffered by male than female, namely the ratio of men and women is 2.1: 1 (10). Study conducted by Yulianda et al (11) showed that male patients (40) diagnosed with cirrhosis more than female (23 patients). The difference number because male has habit to consuming alcohol whis is alcohol is one of material that causes cirrosis. In addition, male who act as the leader in househol will works harder so that they are physically more suspectable to disease (12).

In **Table 1.2** the most participant who suffered from chirrosis with portal hypertension was found in the age 56 – 65 years as many as 8 patients (37%). Cohort study by Vaz J et

al (13), identified 598 chirrosis patients that grouped by age, the highest incidence rate was in the 60-69 years. This is also supported by research conducted by Pineda et al. which suggests that advanced liver fibrosis is more common in old age. A higher degree of fibrosis, which occurs in the liver may be associated with the loss of regenerative and homeostatic capacity of the liver with age. In particular, aged hepatocytes have been implicated in the development of fibrosis and cirrhosis (14). In addition, with age and lifestyle changes, the initially healthy liver will eventually experience cell necrosis (15).

Based on the results of the study on the patient's PMR, we obtained that 22 patients (100%) covered by national health insurance (JKN) (100%) or none of them have private insurance **(Table 1.3).** JKN is part of the National Social Security System (SJSN). The National Social Security System based on Law Number 40 of 2004 aims to ensure that all Indonesians are protected in the insurance system, so that they can meet the basic needs of decent public health (BPJS, 2014). Providing cheap and good quality medicines is the main thing for all JKN patients. The existence of this intervention helps patients to obtain drugs that are safe and have the same quality as brand-name drugs but are cheaper. The role of pharmacists will increase cost efficiency in managing drugs needed in the JKN era. In **Table 2.1** shows the diagnostic data other than portal hypertension. Portal hypertension is an important pathophysiology of cirrhosis, which can lead to an increased risk of death and complications such as hematemesis and/or melena, esophageal varices, ascites, spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy (6). Anemia is defined as a condition in which the body has a decreased number of circulating erythrocytes, or red blood cells. It can also be defined as a decreased hemoglobin concentration or red blood cell mass compared to age-matched controls. As with almost all human laboratory tests, normal value is a statistical term used to define a 95% range of population values (10). Chirrosis patient with a hemostatic imbalance can increased risk of bleeding and a concomitant risk of thrombosis. Patients are at risk for bleeding due to coagulation factor deficiency, thrombocytopenia, platelet dysfunction, and alterations in the fibrinolytic system. The development of hepatic fibrosis can lead to worsening portal hypertension and the formation of portosystemic venous shunts including esophageal varices, gastric varices, and hemorrhoids. Patients with variceal bleeding are also at high risk for infections such as pneumonia, SBP, and urinary tract infections. Hepatic enchepalophaty can occur spontaneously or with precipitating conditions including infection, bleeding, diuretic overdose, electrolyte disturbances, and constipation (9).

Table 3.1 shows the pattern of the use of single therapy as many as 22 patients (100%), propranolol is a nonselective β-blocker (NSBB) that induces decreased cardiac output

and splanchnic vasoconstriction (16). According to the European Association Guideline for the Study of the Liver (EASL), the dose of propranolol is given orally with doses ranging from 10 – 20 mg twice a day. Portal hypertension is a complication of cirrhosis which is the final stage of any chronic liver disease. Portal hypertension can occur when the portal venous pressure (HVPG) measurement is more than 5 mmHg, while patients with HVPG more than 12 mmHg cause variceal bleeding. Propranolol works in two ways to reduce portal venous pressure. First, it blocks the β1 receptor which causes a reduction in cardiac output. Second, it blocks β2 receptors, causing reduced splanchnic blood flow. Propranolol has an effect on HVPG which is a reduction of up to 31% (17).

Table 3.3 shows the percentage pattern of the use of the propranolol switch. The patient has increased portal venous pressure. Portal hypertension occurs when the portal venous pressure is >12 mmHg and if it is more than 12 mmHg complications such as varicose veins and ascites occur (18). Portal pressure if it is above 12 mmHg causes portal hypertension and clinically there is a potential for bleeding (19). The patient on the second day was given Propranolol (2×10 mg) orally. The clinical data showed that blood pressure (150/70), and pulse had increased as well as from laboratory data of erythrocytes (2.7 103/uL) and albumin (2.9 g/dL) decreased. Hypoalbuminemia is thought to play an important role in the pathophysiology of ascites, portal hypertension and a decrease in plasma oncotic pressure, this can lead to changes in the starling balance in the liver microcirculation and the release of fluid into the peritoneal cavity (9). So on the third day until the last day the propranolol dose was increased to (2x40 mg) po in order to overcome portal pressure and prevent bleeding.

Table 3.4 demonstrated the duration of therapy using propranolol in cirrhosis patients with portal hypertension. Propranolol is given orally in doses ranging from 10 – 20 mg twice daily, the dose may be increased every 2 – 3 days until the maximum dose should not exceed 320 mg/day (16). **Table 3.5** shows the length of stay for cirrhosis patients with portal hypertension at Sidoarjo General Hospital. The length of the patient's stay in the hospital depends on the development of the patient's condition. The more severe of complications experienced by the patient, the more complex condition of the patient, the longer the patient's stay in the hospital (9). Based on **Table 3.6** indicate that the condition of patient when he was discharged from hospital was improving as many as 22 patients (100%)

5. CONCLUSION

The pattern of using oral single therapy was 22 patients (100%). The highest use of single therapy was Propranolol (3×10 mg) with 12 patients (52%), Propranolol (2x10 mg) with 10 patients (43%), and Propranolol (2x40 mg) only 1 patient (5%). Interm of switching therapy, only one medication which is Propranolol (2x10 mg switch to Propranolol (2x40 mg).

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