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RESEARCH ARTICLE

The Use of Diuretics on Hepatic Cirrhosis Patient with Ascites

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Abstract

Background: Hepatic cirrhosis with ascites complication increases the mortality up to 50% in a matter of years. Diuretics are a class of drugs that are often used as choices. The pattern of diuretics use of hepatic cirrhosis patient with ascites in the hospital needs to be studied further because if the use is not appropriate, it will potentially lead to drug related problems that affect patient management. Aim: to examine the pattern of diuretics use of hepatic cirrhosis patient with ascites which undergoing treatment in the hospital inpatient unit. Method: a descriptive and retrospective study using medical records. Criteria for inclusion of the sample were (1) Hepatic cirrhosis patient with ascites complication (2) Age> 20 years (3) Receive diuretic therapy (4) Complete medical record. The exclusion criteria were patient who was hospitalized for less than 3 days. Study samples were recorded on the data collection sheet. Sampling with time limited sampling method. Result: The total number of patients who met the inclusion criteria was 45 patients. The diuretics which most used was furosemide, both in single doses and in combination with Spironolactone. The hepatic cirrhosis patient with ascites in this study not only received diuretic therapy, but patient also received other drugs that used to prevent and overcome complication. In drug interaction, the potential use of Spironolactone with Potassium (KCl or KSR) preparation increases the risk of hyperkalemia. Conclusion: Most of the diuretic therapies obtained by hepatic cirrhosis patient with those who were hospitalized which have been in accordance with the available guidelines.

Keywords: *As cites, Drug Related Problems, Diuretics, Hepatic Cirrhosis.*

Introduction

Hepatic cirrhosis is a chronic, irreversible disease and it is associated with significant morbidity and mortality. This disease is one of the highest causes of death in the world with a mortality rate of 1,028,000 every year [1,2]. The most common cause of hepatic cirrhosis in the United States is alcoholic liver disease. In contrast to Indonesia, hepatitis B and C are more prominent causes of cirrhosis compared to alcoholic liver disease.

In addition, hepatic cirrhosis can also be caused by immunological disorders such as autoimmune hepatitis, and the long-term consumption of drugs such as isoniazid, metildopa, amiodarone, dronedarone, methotrexate, tamoxifen, retinol, propyltiouracil, and didanosine for a long time are the causes of hepatic cirrhosis [2].Complication that can occur in cirrhosis patient include ascites, variseal bleeding, and hepatic encephalopathy. Complications that arise related to ascites are spontaneous bacterial peritonitis, hepatorenal syndrome and dilutional hyponatremia. Approximately 50% of Hepatic Cirrhosis patients have ascites complication in the last 10 years and the risk of mortality in cirrhosis patient with ascites complication has increased to 50% in 3 years [3, 5].

The therapy which commonly used for as cites is diuretics. Giving diuretics are usually done in 90% of patients with ascites, especially ascites grade or 4. Diuretic therapy

is carried out along with salt restrictions in the diet. Spironolactone and furosemide are the main pharmacological therapies for ascites. The therapy which usually use is a combination of 100 mg spironolactone and 40 mg furosemide given in the morning. If therapy with spironolactone for two weeks does not provide an adequate response then add furosemide with an initial dose of 20-40 mg/day.

If it is needed, the dose of spironolactone can be increased gradually to 400 mg/day while the dose of furosemide can be increased gradually to 160 mg/day. If the natrium restriction and the providing of high-dose diuretics do not provide a positive response as in refractory ascites, then Large Volume Parascentesis (LVP), Transjugular Intrahepatic Portosystemic Shunt (TIPS), and liver transplantation can be performed [6, 9].

Some diuretics for hepatic cirrhosis with ascites can cause drug interaction and unwanted side effects, such as NSAIDs, which decreases the kidney response to loop diuretics, one of which is furosemide, by inhibiting the formation of prostaglandins so that the vasodilator effect of diuretics will reduce, then the decreasing of natriuresis, sodium retention and hypervolemia can occur.

The drug groups of ACE-Inhibitor (captopril, enalapril) and Angiotensin Receptor Blocker (losartan, telmisartan) have an additive effects if they are used together with potassium sparing diuretics, one of which is spironolactone, so that it can increase the risk of hyperkalemia, cardiac arrhythmia, and cardiac arrest. Side effects that can occur in the use of furosemide are hypokalemia accompanied by metabolic alkalosis, hyponatremia, hypomagnesemia, and hyperuricemia.

Side effects that can occur on the use of spironolactone are hyperkalemia, gynecomastia, gastritis, and gastrointestinal disorders such as nausea and vomiting [10,11]. Evaluation of the diuretic therapy effectiveness is assessed based on the development of the patient's response ie achieving a daily weight loss target up to the fifth day of diuretics giving by 0.3-0.5 kg/day (patient without peripheral edema) and 0.5-1.0 kg/day (patient with peripheral edema), also decreasing a daily abdominal circumference and increasing a daily urine volume. The pattern of diuretics use of hepatic cirrhosis patient with ascites still needs to be studied more deeply because of the possibility of the inappropriate therapy emergence and potentially occur the drug related problems that affect the management of heart failure patient, so an observational study was conducted to examine the pattern of diuretic use of hepatic cirrhosis patient with ascites in the hospital inpatient unit.

Method

The study conducted was non-experimental or observational research that was descriptive retrospective. The study material used health medical record data of patient with a diagnosis of hepatic cirrhosis with ascites who received diuretic therapy in the hospital inpatient unit. The criteria for inclusion of samples were (1) Patients which diagnosed by hepatic cirrhosis with ascites complication (2) Male and female with age of > 20 years old (3) Received diuretic therapy (4) Complete medical record including name, age, type gender, acquired therapy, clinical data and laboratory data. Furthermore, the exclusion criteria were patient who undergoing treatment in the hospital inpatient unit less than 3 days. Sampling was carried out by time limited sampling method.

Samples were taken in the period of January 2013 to March 2017. Data collection was carried out in the medical record room at Universitas Airlangga Hospital, Surabaya, Indonesia. Data analysis was performed based on data obtained from patient medical records. Furthermore, the data obtained from the data collection sheet was entered into the main table then processed and analyzed descriptively in the form of tables, diagrams, graphs or narratives. This study has been examined by the Komisi Etik Penelitian Kesehatan Rumah Sakit Bhayangkara Surabaya and has been declared ethical.

Results

Based on the study result, it was found that 45 patients who met the inclusion criteria and were dominated by male gender (53.33%). Furthermore, the largest age of the patient was in the age group of 45-64 years (75.56%). The three most common complication experienced by patient were

hypoalbumin (26.67%), Anemia (24.44%) and Spontaneous Bacterial Peritonitis (SBP) (20.00%). In the length of stay was in the range of 6-10 days (46.67%), 3-5 days (33.33%) and > 10 days (20.00%).

Pattern of the Diuretics Use on Hepatic Cirrhosis with Ascites

Type of Diuretics

The following will be presented the detailed profile of diuretics.

Table 1: Types of Diuretics

Diuretics		(%)
Group or Class	**Type**	
Potassium-Saving Diuretics	Spironolactone	2,22
Strong Diuretic	Furosemid	17,78
Potassium-Saving Diuretics + Strong Diuretic	Spironolactone + Furosemid	80,00

Diuretic Regimentation

Drug regimens were grouped according to dosage, route, and frequency of the use which can be seen in the following table in detail.

Table 2: Diuretic Regimentation

Drug Name	Dosage dan Frequency	Route	(%)
Spironolactone	1x100 mg	PO	44,44
	3x25 mg	PO	15,56
	3x50 mg	PO	8,89
	1x25 mg	PO	6,67
	1x50 mg	PO	4,44
	3x100 mg	PO	4,44
	2x25 mg	PO	2,22
	2x100 mg	PO	2,22
	1x100 mg	IV	2,22
Furosemid	1x20 mg	IV	57,78
	2x20 mg	IV	26,67
	3x20 mg	IV	24,44
	1x40 mg	PO	4,44
	2x40 mg	PO	2,22
	4x20 mg	IV	2,22
	3x40 mg	IV	2,22

Table 3: Single and Combination Therapy Used

Acqured Therapy	Diuretics Group	Drug Name	(%)
Diuretics Single Therapy	Potassium-Saving Diuretics	Spironolactone 100 mg	15,56
		Spironolactone 25 mg	2,22
		Spironolactone 200 mg	2,22
	Strong Diuretics	Furosemid 20 mg	24,44
		Furosemid 60 mg	11,11
		Furosemid 40 mg	8,89
		Furosemid 80 mg	2,22
Combination Therapy	Potassium-Saving Diuretics + Strong Diuretics	Spironolactone 100 mg – Furosemid 40 mg	24,4
		Spironolactone 100 mg – Furosemid 20 mg	20,00
		Spironolactone 100 mg – Furosemid 60 mg	17,78
		Spironolactone 75 mg – Furosemid 20 mg	15,56
		Spironolactone 200 mg – Furosemid 40 mg	8,89
Combination Therapy	Potassium-Saving Diuretics + Strong Diuretics	Spironolactone 25 mg – Furosemid 40 mg	4,44
		Spironolactone 50 mg – Furosemid 20 mg	4,44
		Spironolactone 50 mg – Furosemid 40 mg	4,44
		Spironolactone 200 mg – Furosemid 60 mg	2,22
		Spironolactone 25 mg – Furosemid 20 mg	2,22
		Spironolactone 50 mg – Furosemid 60 mg	2,22
		Spironolactone 100 mg – Furosemid 120 mg	2,22
		Spironolactone 300 mg – Furosemid 40 mg	2,22
		Spironolactone 300 mg – Furosemid 60 mg	2,22

Drug Therapy Other Than Diuretics

The following can be seen in the table below:

Table 4: Drug Therapy Other Than Diuretics

Complication	Drug Therapy	(%)
Hypoalbumin	Albumin 20%	93,33
Anemia Thrombocytopenia	Transfusion PRC TC	46,67 2,22
Hypokalemia	KCl premix	4,44
	KSR	20,00
Portal Hypertension	Propanolol	31,11
Antibiotics for Therapy of *Spontaneous Bacterial Peritonitis* (SBP) or sepsis	Cefotaxime Ceftriaxone Levofloxacin Ceftazidim Ciprofloxacin Cefixime	60,00 15,56 2,22 2,22 11,11 2,22
Ensefalopati Hepatik (EH)	Lactulose Comafusin Hepar Metronidazole	44,44 2,22 2,22
Variseal Bleeding or Hematemesis Melena (HM)	Omeprazole Ranitidine Sucralfat Vitamin K Lansoprazole Octreotide	73,33 20,00 42,22 24,00 2,22 2,22

Identification of Drug Related Problem (Drp)

Problems of patient with potential drug interaction can be seen in the following table:

Drug Interaction

Table 5: Drug Interaction

Type of DRP	Explanation	Monitoring Parameter	(%)
Spironolactone with Potassium Preparation (KCl or KSR)	Potassium preparations increase the risk of hyperkalemia	Serum potassium levels	24,44

Discussion

Most patients who were hospitalized in the hospital were men. The higher male gender ratio than the female was possibly due to the Hepatitis B Virus (HBV) carrier women which have not been menopause, the production of Anti-HBsAg and Anti-HbeAg antibodies was higher than in men who were also HBV carriers.

The progression time from the hepatitis C virus to become cirrhosis in women was also longer than in men. Therefore, it was stated that men have a higher risk of hepatic cirrhosis than women [12].The results of this study indicate that the highest number of hepatic cirrhosis patient with ascites occurred in the age range of 45-64 years. Age over 50 years was one of the risk factors for cirrhosis. At the age above 50 years, there was a decrease in liver function both in terms of anatomical characterized by a decrease in liver mass, volume, and blood flow. Moreover, there were also occurred the significant cellular changes in hepatocytes and endothelial sinusoids [12, 13].

Complication experienced by hepatic cirrhosis patient other than ascites include Hypoalbumin, Anemia, Hematemesis-Melena (HM), Spontaneous Bacterial Peritonitis (SBP), obstructive jaundice and Hepatic Encephalopathy (EH). Patient with hepatic cirrhosis was prone to hypoalbuminemia due to the decreased albumin production that caused the decreased synthetic liver function [14, 15]. Spontaneous Bacterial Peritonitis (SBP) was a complication that often causes death with a mortality rate of 20-40%. Another complication in hepatic cirrhosis patient was Hepatic Encephalopathy (EH).

In Indonesia, the prevalence of Hepatic Encephalopathy was estimated to occur in 30% -84% of hepatic cirrhosis patient [16, 18]. Cirrhosis patient with ascites can undergo hospitalization with the shortest period of time was 3 days and the longest was 27 days. A study stated that the more complication experienced by cirrhosis patient, the length of stay (LOS) will increase.

Complications of hepatic cirrhosis (other than as cites) that prolong LOS include Spontaneous Bacterial Peritonitis (SBP) and Hepatic Encephalopathy (EH). When compared with data from this study, hepatic cirrhosis patient with the complication which has been mentioned before, it did not always prolong LOS.

For example, in one hepatic cirrhosis patient with complication of as cites, hypoalbumin, and SBP, but only hospitalized within 4 days because the patient died due to shock septic. Whereas the patients with the highest LOS in this study with 27-days stay, were hepatic cirrhosis patient with ascites, hypoalbumin, sepsis and hepatic encephalopathy (EH) [19].

The type of diuretic therapy used by hepatic cirrhosis patient with ascites can be a single diuretic, namely furosemide or spironolactone, or a combination of both. Furosemide has a faster onset of diuresis than spironolactone, which was 30 minutes to 1 hour; its maximum effect was achieved within 1-2 hours. The duration of diuresis lasts for 6-8 hours on the oral route and approximately 2 hours on the IV route. Spironolactone has a gradually increasing onset, maximum diuretic effect achieved on the third day.

The duration of diuresis lasts for 2-3 days until the usage was stopped [9, 20]. There were two diuretics use routes in this study, namely intravenal (IV) and per oral (PO). Dosage and frequency of use depend on the severity of the hepatic cirrhosis electrolyte levels (potassium and serum natrium). Furosemide was the most widely used intravenous route with a daily dose of 20 mg 1x, while spironolactone per oral with a daily dose of 100 mg 1x1.

Recommendation from the Hepatitis C Resource Center Program, furosemide therapy 20-40 mg was used if hyperkalemia occurred, and the dose can be increased to 160 mg per day. As for spironolactone monotherapy, 25 mg, 100 mg, and 200 mg were used. From the three doses, the most widely used was 100 mg. This was in accordance with the AASLD recommendation that the dosage which recommended for initial therapy with spironolactone was 100 mg/day. When compared with the guidelines, the dose used was in accordance with the recommendation [9, 21, 22].In this study besides experiencing as cites complication, the patient also experienced other complication. For this reason, management of hepatic cirrhosis therapy can be divided into two categories, the first category being resolution for complication that has already occurred. The most complication of hepatic cirrhosis besides as cites was hypoalbumin and received 20% of albumin infusion therapy.

In addition, another complication was anemia which was most often treated with Packed Red Cell (PRC). Patient with hypokalemia was treated with KCl premix, or KSR [2, 3, 23]. Spontaneous Bacterial Peritonitis Therapy used adequate broad-spectrum antibiotics to treat three major pathogenic bacteria namely Escherichia coli, Klebsiella pneumoniae, and Pneumococci in patients who suspected of having SBP or having experienced SBP. Cefotaxime 2 gram every 8 hours or other third generation cephalosporin given within 5 days was an effective therapy for SBP. Intravenous ciprofloxacin was also effective as a potential therapy for SBP.

The standard therapy for hepatic encephalopathy was lactulose, a non-absorbable disaccharide that was metabolized by the normal flora of the small intestine become acetic acid and lactic acid, causing a decrease in colonic pH and producing a laxative effect [22].Drug interaction potentially can occur with the use of furosemide and spironolactone. In patient in this study, the drug interaction which potentially occurred included spironolactone if it used along with potassium preparation that was potentially cause hyperkalemia. However, in this study no actual drug interactions were found.

Conclusion

Most of the diuretic therapy use of hepatic cirrhosis patient with ascites in the inpatient installation was in accordance with existing

guidelines. In this study, there was no drug related problem (DRP).

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