



The 6th Asian Academic Society International Conference (AASIC)
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DRUG UTILIZATION STUDY OF DIURETICS IN HEPATIC CIRRHOSIS PATIENT WITH ASCITES AT AIRLANGGA UNIVERSITY HOSPITAL SURABAYA

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ABSTRACT

Ascites is an accumulation of fluid in the peritoneal space and one of the first signs of decompensation of liver disease. Ascites is one of the complications experienced by patients with hepatic cirrhosis. Therapy commonly used for ascites is diuretics, along with salt restriction in the diet. Potassium-sparing diuretics, especially spironolactone and loop diuretics, especially furosemide, are the main pharmacological therapies for ascites. The purpose of this study was to examine the characteristics distribution of hepatic cirrhosis patients, to assess the profile of the use of diuretic drugs during hospitalization, and to determine the possibility of a Drug Related Problem (DRP) on diuretic therapy for patients with ascites at Airlangga University Hospital (RSUA) Surabaya. The research was conducted with non-experimental methods or observations, it was subsequently analyzed descriptively. Data collection was carried out in non-random and time limited sampling in the period of 1 January 2013 - 31 March 2017 in the Inpatient Room of Internal Medicine Department at RSUA Surabaya and was declared as ethically feasible. Based on the results of 45 SH samples with complications of ascites, the most common characteristics of hepatic cirrhosis patients were men by 53.33%, the highest age range was 45-64 years at 75.56%, while the highest complication was hypoalbumin with the percentage of 26.67% and the longest treatment duration was 6-10 days at 46.67%. The therapeutic profile of diuretics in this study, namely the use of furosemide as a single therapy with the percentage of 17.78% and single spironolactone therapy of 2.22% and combination therapy of spironolactone with furosemide with the percentage of 80.00%. The most widely used furosemide was intravenous use with a daily dose of 1x20mg 57.78%, while spironolactone was the most widely used in oral use with a daily dose of 1x100mg 44.44%. Drug Related Problems (DRP) that occurred including potential drug interactions found in concomitant use between spironolactone and potassium preparations with the percentage of 24.44%. No actual drug interactions and side effects were found in this study.

Keywords: Hepatic Cirrhosis, Ascites, Diuretics, Spironolactone, Furosemide.

1. INTRODUCTION

Hepatic cirrhosis is the twelfth highest death cause in the world with a death rate of 1,028,000 each year (WHO, 2013). According to the reports of government public hospitals in Indonesia, the average prevalence of hepatic cirrhosis is 3.5% of all patients treated at Internal Medicine Installation, or an average of 47.4% of all liver disease patients treated (PPHI, 2013). Based on the reports from some general hospitals in Indonesia, it can be seen that the prevalence of hepatic cirrhosis treated in the hospital is about 3.6-8.4% in Java and Sumatra, while in Sulawesi and Kalimantan is less than 1% (Kusumobroto, 2012).

The complications that can be occurred on cirrhosis patients include Ascites, variseal hemorrhage, and hepatic encephalopathy (Dipiro et al, 2015). The complications emerge due to Ascites are spontaneous bacterial peritonitis, hepatorenal syndrome and dilutional hyponatremia (Tasnem et al, 2015). Ascites is the most common complication experienced by cirrhosis patients (Cesario et al, 2013). Approximately, 50% of hepatic cirrhosis patients experience the complication of Ascites in the last 10 years and the risk of mortality in cirrhosis patients with complications of Ascites increased by 50% in 3 years (Padersen et al, 2015). The common therapy used for Ascites is diuretics. The administration of diuretics is usually carried



out on 90% patients with Ascites especially Ascites grade 3 or 4. Diuretics therapy is carried out with salt restriction in the diet (Kusumobroto, 2012).

Increased aldosterone plays a role in Na retention and can develop into Ascites. Drugs that can inhibit the effects of aldosterone are rational treatments for Ascites. Spironolactone is the diuretics commonly used in Ascites therapy. This drug is more suggested because it works slowly and has potassium-sparing effect. Diuretics effect from spironolactone can be seen after 48 hours (Paldosky and Isselbacher, 2000). The indication of minimum effective dose of spironolactone can be obtained by observing the electrolyte concentration of the urine in order to determine the increased level of Sodium and the decreased Kalium that represent the effective competitive problems on aldosterone. In contrast, the development of hyperkalemia might cause the dose of spironolactone should be limited or reduced (Paldosky and Isselbacher, 2000).

Spironolactone and furosemide are the main pharmacological therapy for Ascites. The therapy commonly used is the polytherapy of 100 mg spironolactone and 40 mg furosemide given in the morning (Runyon, B. A., 2012). Patients with mild to moderate Ascites can be treated by using spironolactone 100-200 mg/day. If the therapy of spironolactone for two weeks does not give any good response, then furosemide should be added with the initial dose of 20-40 mg/day. If needed, the dose of spironolactone can be increased gradually up to 400 mg/day and the dose of furosemide can be increased gradually up to 160 mg/day (Biecker, 2011). If the restriction of sodium and the administration of high dose-diuretics do not give any positive response as in refractory Ascites, then it is allowed to perform *Large Volume Paracentesis* (LVP), *Transjugular Intrahepatic Portosystemic Shunt* (TIPS), and liver transplantation (Biecker, 2011).

NSAID drugs reduce kidney response to loop diuretics such as furosemide, by inhibiting the formation of prostaglandins so that the vasodilator effect of diuretics will decrease, there can be a decrease in natriuresis, sodium retention and hypervolemia (Archer¹ et al, 2015). *ACE-Inhibitor* drugs (captopril, enalapril) and *Angiotensin Receptor Blocker* drugs (losartan, telmisartan) can be additive if they are used simultaneously with potassium sparing diuretics, such as spironolactone, so it can increase the risk of hyperkalemia, cardiac arrhythmia, and cardiac arrest (Archer² et al, 2015). The side effects of the use of furosemide include hypokalemia with metabolic alkalosis, hyponatraemia, hypomagnesaemia, and hyperuricemia (Harlan, E. Ives, 2012). The side effects of the use of spironolactone include hyperkalemia, gynecomastia, gastritis, and gastrointestinal disorders such as nausea and vomiting (Archer² et al, 2015).

2. METHODS

This study was conducted by using non-experimental or observational method that was retrospective descriptive through patient medical records. All hepatic cirrhosis patients hospitalized in RSUA became the population and some of the population that fulfilled the inclusion criteria i.e. hepatic cirrhosis patients with Ascites that are given diuretics therapy and hospitalized in RSUA on January 2013 up to March 2017 became the sample of the research.

Patients fulfilled the inclusion criteria as the sample of the study if they meet the criteria i.e. hepatic cirrhosis patients with Ascites complication, male or female ≥ 20 years old given diuretics therapy and the Health Medical record is complete including name, age, gender, therapy given, clinical data and laboratory data. The patients that were hospitalized in RSUA less than three days cannot be the sample of the study.

The sampling techniques was Time Limited Sampling, i.e. taking all data of the Health Medical record of the patients fulfilling the inclusion criteria on January 2013 – March 2017. The variable observed was the hepatic cirrhosis patients with Ascites, age, gender, type of drug, dose, route of use, frequency of administration, duration of use, clinical data (BP, pulse, temperature, RR, urine volume, weight, abdominal circumference), laboratory data on Electrolyte levels (Na, K, Cl), SGOT/AST, SGPT/ALT and Albumin.



3. RESULT

In this study, the researcher collected the Health Medical record of the hepatic cirrhosis patients hospitalized in Internal Medicine polyclinic in Airlangga University Hospital (RSUA) Surabaya in the period of January 1 2013 – March 31 2017, and obtained the sample of the study as many as 157 patients. From the sample, it was obtained 45 patients fulfilled the inclusion criteria i.e. hepatic cirrhosis patients with Ascites given diuretics therapy.

3.1. The Characteristics of the Research Subject

The characteristics of this research subject are the gender, age, and the complication and the length of stay. Below is the characteristics of the 45 hepatic cirrhosis patients with Ascites fulfilled the inclusion criteria.

3.1.1. Profile of Gender

From the 45 hepatic cirrhosis with Ascites in the study, based on the gender of the patients, it was obtained 53.33% male hepatic cirrhosis patients with Ascites and 46.67% female hepatic cirrhosis patients with Ascites. The characteristics of the research subject according to the gender can be seen in **Table 1**.

Table 1 The gender of the hepatic cirrhosis patients with Ascites

No.	Gender	Amount of Patients	Percentage (%)
1.	Male	24	53,33
2.	Female	21	46,67
Total		45	100,00

3.1.2 Profile of Age

According to Ministry of Health of the Republic of Indonesia of 2010, the age range is classified into 4 classifications i.e. young adult (18-24 years old), middle-aged adults (25-44 years old), late adult (45-64 years old) and elderly (>65 years old). The distribution of the age of hepatic cirrhosis with Ascites can be seen in **Table 2**. The average of the age of hepatic cirrhosis patients in this study was 58 ± 10.20 years old. The most hepatic cirrhosis with Ascites in this study was the age range of 45-64 years old 75.56%.

Table 2 The distribution of the age of hepatic cirrhosis patients with Ascites

No.	Age Range	Amount of Patients	Percentage (%)
1.	18-24 years old	0	0,00
2.	25-44 years old	1	2,22
3.	45-64 years old	34	75,56
4.	≥65 years old	10	22,22
Total		45	100,00

3.1.3 Profile of the Complication of Hepatic Cirrhosis

In this study, hepatic cirrhosis patients came with several kinds of complications. The three most common complications experienced by hepatic cirrhosis patients are Hypoalbumin 26.67%, Anemia 24.44%, and Spontaneous Bacterial Peritonitis (SBP) 20.00%. Other complications experienced by hepatic cirrhosis patients with Ascites can be seen in **Table 3**.

Table 3 The complication of hepatic cirrhosis patients with Ascites when being hospitalized

Complication	Amount of Patients	Percentage (%)
Hypoalbumin	12	26,67
Anemia	11	24,44
<i>Spontaneous Bacterial Peritonitis</i>	9	20,00



(SBP)		
Hematemesis-Melena (HM)	8	17,78
Melena	7	15,56
Hepatic Encephalopathy (EH)	4	8,89
Obstructive jaundice	1	2,22

Information: One patient can experience more than one complication

3.1.4 Profile of the Length of Stay in Hospital

The length of stay of the patients in hospital is calculated since the patients are hospitalized until they are discharged from the hospital. The average length of stay was 8 ± 4.81 days. The most hepatic cirrhosis patients with Ascites in this study belonged to the duration of 6-10 days i.e. 46.67%. The length of stay of the patients can be seen in **Table 4**.

Table 4 The length of stay in hospital

Length of Stay	Amount of Patients	Percentage (%)
3-5 days	15	33,33
6-10 days	21	46,67
>10 days	9	20,00
Total	45	100,00

Information:

1. Percentage was calculated from the whole sample of patients
2. One patient might be hospitalized more than once.

3.2. The Design of the Use of Diuretics

3.2.1 The Type of Diuretics

The diuretics given to hepatic cirrhosis patients with Ascites in this study were classified based on the class and type of diuretics that can be seen in **Table 5**. The diuretics mostly used on hepatic cirrhosis patients with Ascites in this study was loop diuretics i.e. furosemide 86.67%, then followed by potassium sparing diuretics i.e. spironolactone 62.22%.

Table 5 The type of diuretics used on hepatic cirrhosis patients with Ascites

Diuretics		Amount of Patients	Percentage of Use (%)
Class	Type		
Potassium sparing diuretics	Spironolactone	1	222
Loop diuretics	Furosemide	8	17.78
Potassium sparing diuretics + Loop diuretics	Spironolactone + Furosemide	36	80.00
Total		45	100.00

Information:

The percentage was calculated based on the amount of hepatic cirrhosis patients with Ascites given diuretics i.e. 45 patients, seen on the whole use of diuretics.

3.2.2 The Diuretic Regimentation

Various types of diuretics given to hepatic cirrhosis patients with Ascites in this study were classified based on the dose, route, and frequency of use that can be seen in **Table 6**. In this study, the diuretics mostly used was spironolactone (1x100 mg) orally on 57.78% then followed by furosemide diuretics (1x20 mg) IV on 44.44%.

Table 6 The route, dose, and frequency of diuretics used by the patients

The Name of Drugs	Dose and Frequency	Route	Amount of Patients	Percentage (%)
Spironolactone	1x100 mg	orally	20	44.44
	3x25 mg	Orally	7	15.56



	3x50 mg	orally	4	8.89
	1x25 mg	orally	3	6.67
	1x50 mg	orally	2	4.44
	3x100 mg	orally	2	4.44
	2x25 mg	orally	1	2.22
	2x100 mg	orally	1	2.22
	1x100 mg	IV	1	2.22
	1x20 mg	IV	26	57.78
	2x20 mg	IV	12	26.67
	3x20 mg	IV	11	24.44
Furosemide	1x40 mg	orally	2	4.44
	2x40 mg	orally	1	2.22
	4x20 mg	IV	1	2.22
	3x40 mg	IV	1	2.22

Information:

The percentage was calculated based on the amount of hepatic cirrhosis patients with Ascites given diuretics i.e. 45 patients, seen on the whole use of diuretics.

In this study, the dose of spironolactone and furosemide diuretics was presented in this following **Table 7**:

Table 7 The monotherapy and polytherapy used by the patients

The Types of Therapy	Class of Diuretics	The Name of Drugs	Amount of Patients	Percentage (%)	
Diuretics monotherapy	Potassium Sparing Diuretics	Spironolactone 100 mg	7	15.56	
		Spironolactone 25 mg	1	2.22	
		Spironolactone 200 mg	1	2.22	
	Loop diuretics	Furosemide 20 mg	11	24.44	
		Furosemide 60 mg	5	11.11	
		Furosemide 40 mg	4	8.89	
Furosemide 80 mg		1	2.22		
Polytherapy	Spironolactone 100 mg – Furosemide 40 mg		11	24.44	
	Spironolactone 100 mg – Furosemide 20 mg		9	20.00	
	Spironolactone 100 mg – Furosemide 60 mg		8	17.78	
	Potassium Sparing Diuretics + Loop Diuretics	Spironolactone 75 mg – Furosemide 20 mg		7	15.56
		Spironolactone 200 mg – Furosemide 40 mg		4	8.89
	Spironolactone 25 mg – Furosemide 40 mg		2	4.44	
	Spironolactone 50 mg – Furosemide 20 mg		2	4.44	
	Spironolactone 50 mg – Furosemide 40 mg		2	4.44	
	Spironolactone 200 mg – Furosemide 60 mg		2	4.44	
	Spironolactone 25 mg – Furosemide		1	2.22	



20 mg			
Spironolactone 50 mg – Furosemide	1		2.22
60 mg			
Spironolactone 100 mg – Furosemide	1		2.22
120 mg			
Spironolactone 300 mg – Furosemide	1		2.22
40 mg			
Spironolactone 300 mg – Furosemide	1		2.22
60 mg			

Information:

1. The percentage was calculated based on the amount of hepatic cirrhosis patients with Ascites given diuretics i.e. 45 patients.
2. One patient might be given more than one diuretics.

3.2.3 Profile of Drugs Therapy Other Than Diuretics

Hepatic cirrhosis patients with Ascites in this study were not only given diuretics therapy but also given drugs used to prevent and overcome hepatic cirrhosis complications used by the patients hospitalized in RSUA Surabaya. The use of drugs other than diuretics can be seen in **Table 8**. Three uses of drugs other than diuretic received by hepatic cirrhosis patients with Ascites are mostly 20% albumin infusion 93.33%, omeprazole 73.33%, and cefotaxime 60.00%.

Table 8 The drugs therapy other than diuretics

No.	Complication	Drugs therapy	Amount of Patients	Persentase (%)
1.	Hypoalbumin	Albumin 20%	42	93.33
2.	Anemia	Transfusion	21	46.67
	Thrombocytopenia	PRC	1	2.22
		TC		
3.	Hypokalemia	KCl premix	2	4.44
		KSR	9	20.00
4.	Portal hypertension	Propanolol	14	31.11
5.	Antibiotics for	Cefotaxime	27	60.00
	<i>Spontaneous Bacterial Peritonitis</i>	Ceftriaxone	7	15.56
	(SBP) therapy or	Levofloxacin	1	2.22
	sepsis	Ceftazidim	1	2.22
		Ciprofloxacin	5	11.11
		Cefixime	1	2.22
6.	Hepatic Encephalopathy (HE)	Lactulose	20	44.44
		Comafusin	1	2.22
		Hepar		
		Metronidazole	1	2.22
7.	Variseal hemorrhage or Melena hematemesis	Omeprazole	33	73.33
		Ranitidine	9	20.00
		Sucralfat	19	42.22
		Vitamin K	11	24.00
		Lansoprazole	1	2.22
		Octreotide	1	2.22

Information:

1. One patient might use more than one co-therapy.
2. The percentage was calculated based on the amount of hepatic cirrhosis patients with Ascites given diuretics i.e. 45 patients.



3.3 The Identification of Drug Related Problems (DRP)

Hepatic cirrhosis patients with Ascites in this study were also given drug therapy other than diuretics for the complication or co-morbidity experienced by the patients. That makes the patients given a lot of drug therapies, so that patients are susceptible to DRP. The problems related to the use of diuretics on hepatic cirrhosis patients with Ascites in this study include potential drug interactions. From the 45 hepatic cirrhosis patients with Ascites who received diuretics, 24.44% of them were with potential drug interactions that can be seen in **Table 9**

Table V.9 Potential drug interaction

Types of DRP	Information	Monitoring Parameter	Amount of Patients	Percentage (%)
Spironolactone with Potassium Preparations (KCl or KSR)	Potassium Preparation increases the risk of hyperkalemia	Serum potassium level	11	24,44

4 CONCLUSIONS

The hepatic cirrhosis patients with Ascites are mostly male 53.33%, in the age of $58 \pm 10,20$ years old with the most age range is 45-65 years old 75.56%. The most common complication experienced is Hypoalbumin, 26.67%. The most common length of stay is 6-10 days i.e. 46.67%. The diuretics commonly used are furosemide polytherapy of spironolactone and furosemide 80.00%. DRP found in this study is potential drug interaction due to the simultaneous use of spironolactone and potassium preparation.

5 SUGGESTION

1. It suggests further study using prospective method in order to understand the condition of patients directly and the problems occurred during the diuretics treatment and be able to directly interact with clinicians and other health workers so complete data can be obtained.
2. It suggest to record the complete health medical record of the patients so monitoring can be performed and it can be used as the source of information for the evaluation to improve hospital services.
3. It suggests a cooperation between physicians, pharmacists and other health workers in optimizing the use of diuretics especially to prevent the development of diuretics resistance and improving the services to the patients.

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