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Original Article

COMPARATIVE EEFFECTS OF SPIRONOLACTONE AND COMBINATION WITH FUROSEMIDE OF ASCITES FLUID AND BLOOD ELECTROLYTE IN CIRRHOSIS

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ABSTRACT

Objective: This study was to compare the effects of spironolactone and combination with furosemide on blood electrolyte levels and ascites fluid in patients with cirrhosis.

Methods: This research was undertaken with prospectively experimental analysis on a limited population in DR. M Djamil General National Hospital, Padang. We include 11 patients with spironolactone used and 13 patients with combination spironolactone-furosemide utilized.

Results: The percentage of patients who experienced blood electrolyte disturbances with the use of spironolactone was hyponatremia 72.72%, hypernatremia 0%, hypokalemia 45.45%, hyperkalemia 9.09%, hypocalcemia 9.09%, hypercalcemia 18.18%. The percentage of blood electrolyte disturbances on the use of a combination of spironolactone-furosemide hyponatremia was 100%, hypernatremia 0%, hypokalemia 23.07%, hyperkalemia 7.69%, hypocalcemia 15.38%, hypercalcemia 0%. A reduction in body weight and abdominal circumference patients before and after use of spironolactone-furosemide combination is significant (p=0.000).

Conclusion: The effects of spironolactone and combination with furosemide to the blood electrolyte levels in this study showed that the highest percentage of impaired blood electrolyte is hyponatremia and hypocalcemia. Spironolactone-furosemide combination therapy for weight-loss and abdominal circumference better than the single use of spironolactone.

Keyword: Cirrhosis, Spironolactone, Furosemide, Ascites, Blood Electrolyte.

INTRODUCTION

Based on the National Vital Statistics Reports published by the Centers for Disease Control and Prevention (Center for Disease Control and Prevention), chronic liver disease and cirrhosis are the main causes that led to the 12th around 26 thousand deaths annually in the US [1]. In Indonesia, prevalence data cirrhosis has not been available, only the reports of several education centers, such as in the hospital DR. Sarjito, Yogyakarta number of cirrhotic patients ranged from 4.1% of patients treated in the Department of Internal Medicine during the period of 1 year (2004) and in Medan in a 4-year period found patients with cirrhosis as many as 819 (4%) patients of all patients The Department of Internal Medicine [2]. In DR. M. Djamil General National Hospital Padang, the number of patients with liver cirrhosis (non-specific) found the data of 220 patients treated during 2009 and 317 patients were dealt with during the year 2010 (unpublished).

Cirrhosis, or end-stage liver disease, can be defined as parenchymal fibrosis that causes liver nodules and liver function changes, as a consequence of prolonged wound healing response to acute or chronic injury to the liver by a variety of causes. Although there are several other causes, most cases of cirrhosis in the world caused by chronic viral hepatitis, or liver injury related to chronic alcohol consumption [3].

Cirrhosis is a severe liver disease, chronic, irreversible and can cause several other diseases such as ascites, hepatic encephalopathy, and death [4]. Therapy of ascites in cirrhosis complications should be done cautiously and gradually due to acid-base imbalance, hypokalemia, or intravascular volume depletion brought about by overly aggressive treatment that may cause disruption of renal function, hepatic encephalopathy and death. Management of ascites involves initial drug sodium intake restriction and use of diuretics to help the excretion of salt and water [5-7]. Low sodium levels associated with the severity of refractory ascites, the magnitude of the rate of fluid accumulation (estimated from changes in the body weight in a few months), the large volume of paracentesis, and impaired renal function, compared with normal sodium levels in serum [8].

Guidelines of the American Association for the Study of Liver Diseases (AASLD) propose to use as a diuretic spironolactone initial first choice for sites [7]. Many diuretics that have been evaluated by clinical practitioners in the United Kingdom and has been designated a diuretic that can be used is spironolactone, amiloride, furosemide, and butadiene [9].

MATERIALS AND METHODS

The study was performed for 4 (four) months, starting from January to April 2013 in the internal medicine ward DR. M Djamil General National Hospital Padang and ethical were approved by ethic commission Polytechnic of Health Ministry of Health Bengkulu. This research was conducted with an experimental analysis and prospectively on a restricted population. We include 11 patients with spironolactone used and 13 patients with combination spironolactone-furosemide used. The type of data used is divided into 2 parts: 1) qualitative data was including treatment was given and the influence of the use of spironolactone and combination spironolactone-furosemide to the blood electrolyte levels and ascites fluid; 2) quantitative data was including the percentage of cirrhosis patients based on age range, the use of drugs spironolactone and combination spironolactone-furosemide in therapy, blood electrolyte levels, abdominal circumference patient, and the patient's weight.

Data sources include medical records of patients who undergoing therapy with liver cirrhosis ascites complications, nursing notes, and medication usage records, laboratory data, and follow the patient's condition directly. The inclusion criteria for this study were all patients with liver cirrhosis with ascites complications with or without capabilities using spironolactone and its combination with furosemide. Exclusion criteria for this study were patients with liver cirrhosis with ascites complications use drugs that affect the levels of electrolyte patients, patients with loss of consciousness, patients inadequately treated 6 to 7 days.

Data were collected by recording the medical record which includes qualitative and quantitative data and the completeness of patient

data (such as age, therapy against the disease, anamnesis, physical examination, laboratory examination, investigation, the patient's weight before and after therapy, the patient's abdominal circumference size before and after therapy, etc). Data taken were transferred to a data collection sheet that has been put in place. Shortage of medical records comes with watching the nurse records, medication records, and follows the patient's condition through the self-visit.

The level of electrolytes (sodium, potassium, and chloride) in the blood using Ion Selective Electrode method (Ion Selective Electrode/ISE) that is employed in the laboratory, ISE method has good accuracy, the coefficient of variation of less than 1.5%. Calibrators trustworthy and possess a serious quality assurance plan. This method is widely used in the emergency laboratory [10].

Data analysis

- **Qualitative analysis**

Data is tabulated and then compared against the criteria established medicinal use. The comparison indicates the effect of the use of spironolactone and its combination with furosemide to the blood electrolyte levels, body weight, and abdominal circumference patients. As a reference used various literature, containing the standard therapy of complications of cirrhosis with ascites, information books AHFS, Martindale, and other supporting literature. Statistical test using SPSS 17 to ascertain the ratio between the effect of spironolactone and its combination with furosemide on body weight and abdominal circumference patients.

- **Quantitative analysis**

Data tabulated include the percentage of cirrhotic patients with ascites of complications based on age range, the use of spironolactone and its combination with furosemide therapy, blood electrolyte levels, abdominal circumference patient, and the patient's weight.

RESULTS

The number of cirrhotic patients with ascites complications treated with spironolactone or, in combination with furosemide during the study period a total of 24 patients was comprised of 37.5% males and 62.5% of women. Based on age range, the patient is classified as follows: <30 years (8.33%), 31-40 years (20.83%), 41-50 years, (20.83%), 51-60 years (16.66%), and>60 years (33.33%). The number of patients with cirrhotic patients with ascites of complications is grouped based on the use of diuretic therapy is the therapeutic use of spironolactone 45.84% and the use of combination therapy of spironolactone-furosemide 54.16%. The percentage of patients of cirrhotic patients with ascites from complications caused impaired blood electrolyte on the role of spironolactone is as follows hyponatremia 72.72%, hypernatremia 0%, hypokalemia 45.45%, hyperkalemia 9.09%, hypocalcemia 9.09%, hyperchloremia 18.18%. While the combination therapy of spironolactone-furosemide causing hyponatremia electrolyte disturbances following a 100%, hypernatremia 0%, hypokalemia 23.07%, hyperkalemia 7.69, hypochloremia 15.38%, hyperchloremia 0%.

Table 1: A parameter is a characteristic of a population

Variable	n (%)
Sex	
Male	9(37.5)
Woman	15(62.5)
Age (Years)	
<30	2(8.33)
31-40	5(20.83)
41-50	5(20.83)
51-60	4(16.66)
>60	8(33.33)
Diuretic	
Spironolactone	11 (45.84)
Spironolactone-Furosemide	13 (54.16)

Table 2: Comparing the effects of spironolactone or in combination with furosemide on blood electrolyte levels

Electrolyte disturbance	Spironolactone (n=11)	Spironolactone–Furosemid (n=13)
Hyponatremia	72.72 %	100 %
Hypernatremia	0 %	0 %
Hypokalemia	45.45 %	23.07 %
Hyperkalemia	9.09 %	7.69 %
Hypochloremia	9.09 %	15.38 %
Hyperchloremia	18.18 %	0 %

• Effect of spironolactoneon body weight and abdominal circumference

From the observations showed a reduction in body weight and abdominal circumference patients. The average weight of patients before the use of spironolactone is 5.52±50.45 kg while after a single use of spironolactone has an average weight 47.54±5.76 kg. The correlation between the two variables showed 0.984 (P=0.000), taken into account these results showed that the correlation between body weight before and after use of spironolactone is very closely related and totally real. T value is 9.238 (P=0.000) then H0 is denied, or body weight before and after use of spironolactone relatively different. In other words, the use of spironolactone in the weight loss effect is unaffected.

Abdominal circumference average patient before use of spironolactone was 98.90±4.36 cm while the use of spironolactone after having abdominal circumference average of 95.54±3.77 cm. The correlation between the two variables showed 0.979 (P=0.000). Take into account these results showed that the correlation between abdominal circumference before and after use of spironolactone is very closely related and totally real. T value is 10.684 (P=0.000) then H0 is denied, or abdominal circumference before and after use of spironolactone relatively different. In other words, the use of spironolactone effects in decreasing abdominal circumference significantly.

• The effect of the combined use of spironolactone-furosemide on body weight and abdominal circumference

The average weight of patients before the use of spironolactone-furosemide was 54.23±10.95 kg while after use of spironolactone-furosemide has an average weight 50.69±10.92 kg. The correlation between the two variables showed 0.995 (P=0.000), taken into account these results showed that the correlation between body weight before and after use of spironolactone-furosemide is very closely related and totally real. T value is 11.324 (P=0.000) then H0 is denied, or body weight before and after the use of a combination of spironolactone-furosemide relatively different. The use of a combination of a spironolactone-furosemide effect on weight-loss significantly.

Abdominal circumference average patient before use of spironolactone-furosemide was 108.92±20.70 cm, whereas after use spironolactone-furosemide has an average abdominal circum ference 102.46±20.97 cm. The correlation between the two variables showed 0.987 (P=0.000). Take into account these results showed that the correlation between abdominal circumference before and after use of spironolactone-furosemide is very closely related and totally real. T value is 6.992 (P=0.000) then H0 is denied, or abdominal circumference before and after the use of a combination of spironolactone-furosemide relatively different. Use of spironolactone-furosemide effect in decreasing abdominal circum ference significantly.

DISCUSSION

From the observation of the 24 samples of complications patient of liver cirrhosis and ascites utilizing therapy of spironolactone and its combination with furosemide grouped by sex obtained percentage of 37.5% males and 62.5% of women. These data provide an overview of the characteristics of the population and the differences between men and women, where the percentage of female patients

is higher than the number of male patients. The incidence in patients with liver cirrhosis in Indonesia showed more prevalent in men compared with women of about 1.6: 1 with the highest average age between 30-59 years age group with a peak around 40-49 years [11]. Opinion this is also supported by another study conducted by Sudoyo, *et al.* in 2006, liver cirrhosis is more common in men than women by a ratio of 2.4: 1 [2].

Age or age is one variable that is always examined in the assessment of population characteristics. The numbers of events or pain almost all circumstances show an association with age. With increasing age, a person will be followed by a decrease in all organ functions so that the future elderly will reduce the body's resistance or susceptibility to disease. In this study obtained data on the characteristics of the population by age range, which is as follows: <30 years, 8.33%, 31-40 years, 20.83%, 41-50 years, 20.83%, 51-60 years 16.6%, and>60 years 33.33 %. The number of elderly patients affected by impaired liver function due to liver blood flow in patients aged>60 years was reduced by 50-60% compared to younger patients around 20-30 years [12]. The ability of the liver to metabolize the same drug will not be built on differences in age for all kinds of drugs. A history of liver disease in the elderly should be referred back for drug dosing elimination primarily through the liver [12]. The results of Angeli, *et al.*, that low levels of sodium in the serum were not associated with age, gender, or etiology of liver cirrhosis, but more common in patients with severe liver failure, namely in patients with Child-Pugh scores class C [8].

Grouping of observation data for patients receiving diuretic spironolactone therapy 45.84% and the use of combination therapy spironolactone-furosemide 54.16%. A selection of spironolactone therapy alone or in combination with furosemide was decided built on the severity of the patient's ascites. Management of ascites involves initial drug sodium intake restriction and use of diuretics to help the excretion of salt and air [5, 7].

Successful treatment is dependent on the patient's ascites accurate diagnosis based on the cause of ascites [13]. Components of general therapy in patients with liver cirrhosis ascites complications are to avoid the use of the class of drugs-NSAIDs (Non-Steroidal Antiinflammatory Drugs). This class of drugs inhibits the synthesis of prostaglandins, causing vasoconstriction in the kidneys, reducing the diuretic response, and hosts the emergence of acute renal failure [14].

Diuretics are divided into 2 main groups based on place of work. The first group inhibits N^+-K^+-Cl^-co-transporter in the Loop Henle that furosemide and budgeting. The use of furosemide in cirrhotic patients with ascites of complications is used as adjunctive therapy spironolactone use because it is less effective when used singly. Furosemide can be used as an adjunct therapy when the use of single dose spironolactone was 400 mg/day was not effective [15]. Group thiazides inhibit sodium in the distal tubules, have a prolonged half-life time, can lead to hypotension, and are not recommended in the treatment of ascites [16].

The second group is spironolactone (aldosterone antagonist), amiloride, and triamterene inhibits sodium reabsorption in the distal tubules and collecting ducts. This class is the primary option in the treatment of ascites due to liver cirrhosis. Aldosterone antagonist class is small, but potassium-sparing natriuretic. There are two therapies that can be utilized at the beginning of spironolactone are single, or a combination of spironolactone with furosemide. Both treatment options were selected founded on the degree of ascites [17-18].

The use of spironolactone starts with a single dose of 50-100 mg/day based on the patient's degree of ascites. If the clinical response after 3-4 days is not sufficient (reduction in body weight of less than 300 g/day), increased dose of 100 mg/day every 4 days to a maximum dose of 400 mg/day, to avoid the occurrence of hyperkalemia. Shortage of clinical response indicated to examine the levels of sodium in the urine, owing to higher levels would be advisable to reduce foods high in sodium. If the clinical response is not sufficient or does not reply to the use of a single spironolactone (200 mg/day) or hyperkalemia occurs, can be added to the loop diuretics such as furosemide at a dose of 20-40 mg/day [16].

The long-term use of spironolactone can cause gynecomastia pain. It must be replaced with amiloride 10-15 mg/day. But the amiloride less effective than spironolactone. Another reason that may weaken the effect of diuresis on the use of diuretics when used in conjunction with non-steroidal anti-inflammatory, inhibitor angiotensin converting enzyme or receptor blocker angiotensin [19].

Effect of spironolactone on electrolyte disturbance the data obtained in this study that the incidence of high blood electrolyte disturbance hyponatremia, which is 75.72%, followed by hypokalemia 45.45%, hyperchloremia 18.18%, hyperkalemia 9.09%, hypochloremia 9.09%, and hypernatremia 0%. While the effect of using a combination of spironolactone-furosemide therapy in patients with liver cirrhosis and ascites complications shows the percentage incidence is highest blood electrolyte disturbance hyponatremia is 100%, then followed by hypokalemia 23.07%, hypochloremia 15.38%, hyperkalemia 7.69%, hypernatremia and hyperchloremia 0%.

From the data obtained it can be concluded that the incidence of hyponatremia, and hypochloremia more common in the use of spironolactone-furosemide combination therapy compared with a definite use of spironolactone. While electrolyte disturbances in hypokalemia, hyperkalemia, and hyperchloremia more common in single spironolactone use of the use of combination therapy spironolactone-furosemide. In the present study found no interference hypernatremia on the use of spironolactone in both single and also on the use of combination therapy of spironolactone-furosemide. This is corroborated by data from the literature concerning electrolyte disturbance caused by the use of spironolactone and its combination with furosemide. Based on the research results of Angeli, *et al.*, that nearly half the patients with liver cirrhosis patients had serum sodium levels below normal [8].

The side effects of spironolactone can cause hyperkalemia and hyponatremia and side effects of furosemide are the case is on fluid and electrolyte balance, including hyponatremia, hypokalemia, and alkalosis hypoglycemic after using large doses and prolonged use [9]. Side effects due to the use of spironolactone inhibit aldosterone action work competitively in distal tubules resulting in excretion of sodium (Na^+) and enhanced excretion of potassium (K^+) decreases. While the mechanism of action of furosemide is tantamount to inhibit reabsorption of sodium (Na^+) and chloride (Cl^-) in the proximal tubules and distal tubules, and especially in the loop Henle. Disadvantages initiate therapy with a combination of routine laboratory monitoring is required [17]. Hyponatremia occurs in approximately 20-30% in cirrhotic patients with ascites is determined by the concentration of sodium<130 mEq/l [8, 20].

The low serum sodium levels in patients with liver cirrhosis associated with the severity of ascites and severity of the hepatic encephalopathy condition, spontaneous bacterial peritonitis, and hepatomegaly syndrome [8]. Hypokalemia should be avoided in patients with liver cirrhosis and ascites due to decreased potassium can increase the production of ammonia and allow for hepatic coma. To be useful electrolyte monitoring, the original sample should be taken before the administration of diuretic therapy [21].

Monitoring body weight and abdominal circumference every day has to be done. To prevent the risk of renal impairment, the maximum reduction of body weight in 0.5 kg/day or 1.0 kg/day in patients with edema [16]. Based on the results of research on patient weight that uses a single spironolactone is 50.45 kg before therapy and 47.54 kg, after therapy resulted in an average weight-loss, is 2.91 kg/7 days (0.42 kg/day), the use of combination therapy with spironolactone-furosemide before therapy 54.23 kg and post-therapy 50.69 kg resulted in an average weight-loss 3.54 kg/7 days (0.50 kg/day). Built on the above shows the use of a combination of spironolactone-furosemide more in line with the literature. The occurrence of ascites in patients with portal hypertension is the result of the sodium and water retention in the kidneys. The maximum rate of reduction of fluid should be 300-500 ml/day when spending more adaptable with diuretics (weight-loss>0.75 kg/day) can cause fluid depletion and azotemia [16].

Table 3: Comparison of the effects of the single use of spironolactone with combination spironolactone-furosemide on body weight

Variable	Spironolactone (n=11)	Spironolactone-Furosemide (n=13)
Average Body Weight		
Before	±50.45 kg	±54.23 kg
After	±47.54 kg	±50.69 kg
Correlation	0.943	0.995
T value	9.238	11.324
Significancy (P)	0.000*	0.000*
*t-test Independent (P<0.005)		

Table 4: Comparison of the effects of the single use of spironolactone with combination spironolactone-furosemide to abdominal circumference

	Spironolactone (n=11)	Spironolactone–Furosemide (n=13)
Abdominal circumference		
Before	±98.90 cm	±108.92 cm
After	±95.54 cm	±102.46 cm
Correlation	0.979	0.987
T value	10.864	6.992
Significancy (P)	0.000*	0.000*
*t-Test Independent (P<0.005)		

CONCLUSION

The effects of spironolactone and combination with furosemide to the blood electrolyte levels in this study showed that the highest percentage of patients with impaired blood electrolyte is hyponatremia and hypocalcemia. Spironolactone use of single and combination with furosemide significant effect on the reduction of ascites fluid on the observed weight and abdominal circumference patients before and after the use of diuretics. Spironolactone-furosemide combination therapy for weight loss and abdominal circumference is better than the single use of spironolactone.

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CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Minino AM, Heron MP, Smith BL. Deaths: preliminary data for 2004. Natl Vital Statistics Reports 2006;54:1-49.
2. Sudoyo AW, Bambang S, Idrus A, Marcellus SK, Siti S. Buku Ajar Ilmu Penyakit Dalam. 4th ed. Jakarta: Pusat Penerbitan Departemen Ilmu Penyakit Dalam. Fakultas Kedokteran Universitas Indonesia; 2007.
3. Friedman SL. Liver fibrosis from bench to bed-side. J Hepatol 2003;38(Suppl):S38-S53.
4. Dipiro JT. Pharmacotherapy: A Pathophysiologic Approach. 6th ed. US: McGraw-Hill Companies; 2005.
5. Suzuki H, Stanley AJ. Current management and novel therapeutic strategies for refractory ascites and hepatorenal syndrome. QJM 2001;94:293-300.
6. Moore KP, Wong F, Ginès P. The management of ascites in cirrhosis: report on the consensus conference of the international ascites club. Hepatology 2003;38:258-66.
7. Runyon BA. Practice guidelines committee: american association for the study of liver diseases (AASLD). Management of adult patients with ascites due to cirrhosis. Hepatology 2004;39:841-56.
8. Angeli P, Wong F, Watson H, Gin`es P. The CAPPS Investigators. Hyponatremia in cirrhosis: results of a patient population survey. Hepatology 2006;44(6):1535-42
9. Sweetman. Martindale: The complete drug reference. London: Chicago Pharmaceutical Press; 2009.
10. Klutts JS, Scott MG. Physiology and disorders of Water, Electrolyte, and Acid-Base Metabolism In: Tietz Text Book of Clinical Chemistry and Molecular Diagnostics 4th ed. Vol. 1. Philadelphia: Elsevier Saunders Inc; 2006. p. 1747-75.
11. Sutadi SM. Sirosis Hepatitis, Internal Medicine of Medical Faculty Sumatera Utara University; 2003.
12. Katzung BG. Farmakologi dasar dan klinik. 8th ed. Jakarta: Salemba Medika; 2004.
13. Runyon BA. AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009;49:2087-107.
14. Sood, Rita. Ascites: Diagnosis and Management. J Indian Acad Clin Med 2004;5(1):81-8.
15. Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. Gut 2006;55(Suppl VI): vi1–vi12.
16. James SD, Anna SF, Lok AK, Burroughs E, Jenny H. Sherlock's Diseases of the Liver and Biliary System. 12th ed. Edited by Blackwell Publishing Ltd; 2011.
17. Santos J, Planas R, Pardo A. Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety. J Hepatol 2003;39:187–92.
18. Angeli P, Fasolato S, Mazza E. Combined versus sequential diuretic treatment of ascites in nonazotemic patients with cirrhosis: results of an open randomized clinical trial. Gut 2010;59:98–104.
19. Vlachogiannakos J, Tang AKW, Patch D. Angiotensin converting enzyme inhibitors and angiotensin II antagonists as therapy in chronic liver disease. Gut 2001;49:303–8.
20. Planas R, Montoliu S, Balleste B. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol 2006;4:1385–94.
21. Gentilini P. Update on ascites and hepatorenal syndrome. Dig Liver Dis 2002;34:592-605.