The Efficacy of Low Dose Captopril Adjuvant for Natriuresis in Patients with Liver Cirrhosis with Ascites Who Have Received Furosemide and Spironolacton

Suyatmi, A. Bantar Suntoko, F. Sumanto PM, Hirlan

Sub Division Gastroentero Hepatology, Department of Internal Medicine, Medical Faculty, Dipenogoro University/ Dr. Kariadi General Hospital, Semarang - Indonesia

ABSTRACT

Background: *The ideal therapy for ascites in liver cirrhosis is a low sodium diet and a combination of furosemide and spironolacton. However, this still sometimes does not produce satisfactory results, even after increasing the dose of the diuretic. Such failure occurs due to the influence of the Renin Angiotensin Aldosterone (RAA) system. Low doses of ACE inhibitors (captopril) should improve renal blood flow and increase filtration at the glomeruli, thus increasing natriuresis without causing haemodynamic imbalance.*

Study aim: *To discover the natriuretic and diuretic effects of low dose captopril adjuvant in patients with liver cirrhosis who have received furosemide and spironolacton by measuring urinary sodium and 24-hour urine output.*

Materials and method: *This study was conducted on in- and out- patients with liver cirrhosis and Ascites at the Dr. Kariadi Central Public Hospital, Semarang, who met the inclusion and exclusion criteria. The study took place from June 1st, 1997 to March 31st, 1998, and included 40 cases of liver cirrhosis with ascites.*

Study design: *Open comparative randomized clinical trial with permuted blocks.*

All of the patients received a low fat diet, 40 mg of furosemide, 3x50 mg of spironolacton for 2 weeks, and patients with a urinary sodium level was below 80 mEq/L were randomized into two groups: group A receiving 3 x 6.25 mg of captopril, and group B receiving standard therapy.

Results:

Variable	Pre- treatment	Post – treatment	p
Group A :			
Urinary sodium level (meq/L)	65.450 ± 16.577	109.950 ± 49.109	0.001
24-hour urine output (cc)	1138.750 ± 480.438	1381.250 ± 394.441	0.004
Group B:			
Urinary sodium level (meq/L)	68.30 ± 12.85	91.750 ± 64.04	0.103
24-hour urine output (cc)	1390 ± 448.27	1392.50 ± 713.46	0.988

The pre- and post- treatment results for Group A were significantly different.

The pre- and post- treatment results for Group B were not significantly different.

Conclusion: Low dose (3 x 6.25 mg) captopril adjuvant in patients with liver cirrhosis and ascites who have received standard doses of furosemide and spironolacton could increase natriuresis and diuresis without causing haemodynamic imbalance.

Key words: *Captopril, liver cirrhosis, ascites*

INTRODUCTION

Ascites is the most common complication of liver cirrhosis. Ascites in a patient with liver cirrhosis is an indication for hospitalization and an indication a poor prognosis, which complicates management.[1]

Ascites and edema in a patient with liver cirrhosis occur through a complex mechanism that has not been completely understood. Currently, most experts agree that development of ascites in patients with liver cirrhosis depends on 2 factors: local factors that create fluid accumulation in the abdominal cavity, and systemic factors responsible for changes in the cardiovascular and renal system, causing fluid and sodium retention. Those two factors are directly related with portal hypertension, hypoalbuminemia, the sympathetic nervous system, and renal factors through the renin angiotensin aldosterone (RAA) system, and arginine vasopressin.[2,3,4]

Fluid and sodium retention reduces filtration at the glomeruli, which in turn aggravates ascites.[5,6] Continuous neurohormonal activation would result in more evident changes in renal function, finally generating the hepatorenal syndrome.[2,4]

Patients with mild and moderate ascites usually manage with conventional medical treatment in the form of a low sodium diet of 1-1.5 gram/day and diuretics.[7] A combination of furosemide and spironolacton increases natriuresis and diuresis and minimizes hyperkalemia due to spironolacton.[7,8] The outcome of the standard therapy is often unsatisfactory, even with increased doses of diuretics, causing refractory ascites. Ascites is usually labeled as refractory if the patient's body weight falls less than 200 g/day for 4 days or if sodium excretion is less than 50 meq/day with a dose of 400 mg/day of spironolacton and 160 mg /day of furosemide.[9]

The outcome of adjuvant diuretics varies, including towards the hepatorenal syndrome. If such treatment fails, repeated ascites puncture is conducted, even though this also fails to improve the patient's survival rate.[7,10] Surgical intervention is performed on 5 to 10% of patients with refractory ascites or with hepatorenal syndrome. Surgical intervention has an efficacy rate of 100%, with the possibility of inducing hepatic coma.[2,11]

Constant stimulation on the RAA system increases diuretic requirement. Changes in the blood flow of the renal cortex causes the diuretics to be ineffective. Suppression of the RAA system by ACE inhibitors (captopril) would improve renal blood flow.[12] Low dose captopril adjuvant would reduce the dose of the diuretics and may be used as an alternative adjuvant therapy to the standard treatment.[13] Since there are still only few studies on this, and the authors found no reports of such study conducted in Indonesia, we decided to perform this preliminary study.

STUDY AIM

To determine the natriuretic and diuretic effects of low dose captopril adjuvant in patients with liver cirrhosis and ascites who have received spironolacton and furosemide by measuring urinary sodium and 24-hour urine output.

MATERIALS AND METHODS

The study design chosen was open comparative randomized clinical trial with random permuted blocks.

The study was conducted on in- and out- patients with liver cirrhosis and ascites at the Dr. Kariadi Central Public Hospital, Semarang, who met the criteria, from June 1st, 1997 until March 31st, 1998. Patients who met the study criteria were male and female, over 18 years of age, who suffered from liver cirrhosis and grade II or III ascites. Drugs that could influence the outcome of the study, such as propanolol, nitrates, and NSAIDs, were terminated a week prior to the commencement of the study. The patients in this study were willing to be a volunteer for the study. Exclusion criteria were as follows: creatinine clearance of less than 30 cc/minute, systolic blood pressure of less than 95 mmHg, incontrollable infection, connective tissue disorder.

Sample size: based on literature, the success rate of therapy is 50%. In this study, a success rate of 70% was expected. Based on the formula, 240 subjects were required as sample.[14] In this preliminary study, 40 people were examined.

Data collection and study procedure

All patients who were included as study sample received the following therapy for two consecutive weeks: a low sodium diet of 1.5-2 g/day, 40 mg/day of furosemide, and 3x6.25 mg of spironolacton/day. On the 15th day, the following measurements were taken: bodyweight, blood pressure, pulse rate, abdominal circumference, 24-hour urine volume, 24-hour urinary sodium, blood sodium, potassium, albumin, ureum, and creatinine levels. Complaints during treatment were recorded. Patients with a urinary sodium level of less than 80 mEq/l were then randomized.

The patients were divided into 2 groups. Group A received an adjuvant of 3 x 6.25 mg of captopril/day. Group B received no additional therapy. After two weeks, the same clinical and laboratory evaluation was con-

ducted.

The diagnosis of liver cirrhosis was based on clinical findings, laboratory examinations, and ultrasound findings. The degree of cirrhosis is based on the Child-Pugh criteria.

Data analysis: Collected data were then tabulated and coded for analysis using the SPSS statistical program for PC. The age, sex, complaints, and clinical findings were displayed descriptively. For the variables of body weight, abdominal circumference, blood pressure, 24-hour urine volume, 24-hour urinary sodium, laboratory evaluation before and after randomization, as well as the degree difference is analyzed using paired group T test, and is considered significant if $p<0.05$.

RESULTS

From June 1997 until 31 March 1998, there were 123 patients with liver cirrhosis diagnosed. Seventy-three patients suffered from ascites. Forty patients met the inclusion criteria. The randomized Group A consisted of 20 patients, and Group B consisted of 20 patients. Twenty-patients (52.5%) were male, and 19 (47.5%) female. The age ranged from 25 – 64 years, mostly 40 – 49 years of age (14 patients - 35%). The average age for Group A was 50.35 (± 8.89). The average age for Group B was 49.01 (±6.73).

The most common Child – Pugh score for Group B was score B, in 11 patients (47.8%). The most for Group B was score B, in 12 patients (52.2%). No significant difference was found between group A and B ($p > 0.05$).

Complaints during treatment: (Table 1)

In Group A, 5 patients complained of cough (25 %). Two people complained of confusion (10%) and 2 complained of itching (10%). Nausea, muscle cramps, and diarrhea were each reported by one person. For Group B: 1 person complained of cough, but the same patient also suffered from lung tuberculosis. One person complained of arthralgia, but the person also suffered from osteoarthritis.

Table 1 Distribution of Symptoms during Treatment

Symptom	Group A	%	Group B	%	Total
Confuse	2	100.0	0	0.0	100.0
Cough	5	83.3	1	16.7	100.0
Athralgia	1	50.0	1	50.0	100.0
Itching	2	100.0	0	0.0	100.0
Nausea	1	100.0	0	0.0	100.0
Cramp	1	100.0	0	0.0	100.0
Diarrhea	1	100.0	0	0.0	100.0

The pre- and post therapy clinical parameter for group A can be found in Table 2, group B in Table 3.

Table 2 Clinical parameter Pre- and Post-treatment (Group A)

Variable	Pre	Post	p
Syst. BP (mmHg)	115.500 + 14.681	103.250 + 8.777	0.001
Diast BP (mmHg)	70.500 + 6.863	68.0 + 6.959	0.135
Body weight (kg)	55.125 + 13.487	53.925 + 12.113	0.148
Abdom. Circ. (cm)	87.800 + 12.478	86.250 + 11.008	0.162
Na-urine (meq/L)	65.450 + 16.577	109.950 + 49.109	0.001
Vol.Urine (mL/24h)	1138.750 + 480.438	1381.250 + 394.441	0.004

Table 3 Clinical parameter Pre- and Post-treatment (Group B)

Variable	Pre	Post	p
Syst. BP (mmHg)	114.5 ± 12.34	115.50 ± 11.46	0.58
Diast. BP (mmHg)	74.00 ± 5.98	75.80 ± 6.05	0.19
Body weight (kg)	52.80 ± 8.41	51.62 ± 8.72	0.25
Abdom. Circ. (cm)	84.00 ± 7.98	82.88 ± 7.93	0.078
Na-Urine (meq/l)	68.30 ± 12.85	91.75 ± 64.06	0.103
Vol.Urine (mL/24 h)	1390.50 ± 448.27	1392.50 ± 713.46	0.988

The systolic blood pressure for group A dropped significantly from 115 ± 14.68 to 103.25 ± 8.78 ($p < 0.001$). While the systolic blood pressure for group B showed an insignificant increase from 114.5 ± 12.34 to 115.5 ± 11.46 ($p > 0.05$).

The diastolic blood pressure for group A dropped insignificantly from 70.5 ± 6.86 to 68.0 ± 6.96 ($p > 0.05$). The diastolic blood pressure for group B did not show a significant increase.

The average bodyweight for group A was reduced insignificantly from 55.125 ± 13.487 to 53.925 ± 12.113 ($p > 0.05$). The average body weight in Group B was reduced from 52.8 ± 8.41 to 51.62 ± 8.72 ($p>0.05$). Thus, there was no significant difference in bodyweight reduction between group A and B. Even though the average abdominal circumference for group A and B showed a reduction, there was no significant difference in the two. (Group A from 87.80 ± 12.48 to 86.25 ± 11.0 ($p >$ 0.05) Group B from 84.0 ± 7.98 to 82.88 ± 7.93 ($p >$

0.05))

The urinary sodium level for group A was significantly increased from 65.45 ± 16.58 to 109.95 ± 49.11 ($p < 0.001$). The urinary sodium level for Group B was insignificantly increased from 68.30 ± 12. 85 to 91.75 ± 64.06 ($p > 0.05$). This shows that captopril significantly increases natriuresis.

The average 24-hour urine volume 24 for group A showed a significant increase from 1138.75 ± 480.438 to 1381.25 ± 394.44 ($p < 0.05$). There was no significant change in Group B, from 1390.50 ± 448.27 to 1392 ± 713.46 ($p > 0.05$). This demonstrates a significant difference in an increase in diuresis between group A and B.

Laboratory changes: Na, K, ureum, creatinine, albumin for group A can be found in table IV, and group B in table 5. The average blood sodium level for group A showed an insignificant change, from 138.95 ± 7.326 to 141.20 ± 8.97 ($p > 0.05$). The average blood sodium level for group B showed an insignificant change, from 141.85 ± 6.62 to 137.25 ± 6.41 ($p > 0.05$).

Table 4 Laboratoric Parameter Pre- and Post-treatment (Group A)

Variable	Pre	Post	p
Natrium (meq/L)	138.950 ± 7.236	141.200 ± 8.971	0.359
Kalium (meq/l)	4.337 ± 0.724	4.534 ± 1.012	0.202
Ureum (mg%)	42.5665 ± 24.667	56.511 ± 44.839	0.073
Creatinin (mg%)	1.174 ± 0.450	1.356 ± 0.622	0.020
Albumin (mg%)	3.395 ± 0.78	3.470 ± 0.728	0.419

Table 5 Laboratoric Parameter Pre- and Post-treatment (Group B)

Variable	Pre	Post	p
Natrim (meq/L)	141.85 ± 6.62	137.25 ± 6.41	0.061
Kalium (meq/L)	4.1375 ± 0.54	4.28 ± 1.17	0.67
Ureum (mg%)	32.99 ± 12.46	44.09 ± 20.98	0.01
Creatinin (mg%)	1.10 ± 0.32	1.18 ± 0.38	0.28
Albumin (mg%)	3.34 ± 0.82	3.53 ± 0.80	0.063

The blood potassium levels for group A and B showed a slight increase, which was insignificant. The blood ureum level for group A increased from 42.57 ± 24.67 to 56.51 ± 44.84. yet this increase was not significant ($p > 0.05$). The increase in Group B was significant, from 32.99 ± 12.46 to 44.09 ± 20.98 ($p < 0.001$). The increase in blood ureum level was significant in patients who did not receive captopril adjuvant. The average blood creatinine for group A showed a significant increase from 1.174 ± 0.45 to 1.356 ± 0.622 ($p < 0.05$). There was an insignificant change in Group B, from 1.1 ± 0.32 to 1.18 ± 0.38 ($p > 0.05$). The average albumin level increased significantly in both group A and B ($p > 0.05$) (Group A from 3.395 ± 0.78 to 3.47 ± 0.728; Group B from 3.34 ± 0.82 to 3.53 ± 0.80).

DISCUSSION

Development of ascites in patients with liver cirrhosis is a complex event. Two important factors that play a role in the development of ascites are local and systemic factors.[2,3,4] Local factors include liver sinusoidal flow and the capillary blood system of the intestines, which are responsible for fluid accumulation in the abdominal cavity. A systemic factor still believed to play a role is the peripheral vasodilatation theory, which activates the three vasoconstriction systems: the RAA system, arginin-vasopressin, and the sympathetic nervous system. These three systems cause fluid and sodium retention, causing a reduction in glomerulofiltration, aggravating ascites.[5,6] Administration of a low dose of captopril is expected to inhibit these three vasoconstriction systems, thus improving natriuresis and diuresis.

The subjects of this study were 40 patients with liver cirrhosis and ascites, with a male to female ratio of 1.1:1. The age ranged from 25-64 years, the most being 40-49 years (35%). There was no significant difference between the two groups. The most common Child-Pugh score found was a score B, which indicated moderate liver disorder, followed by scores A and C.

A common complaint that occurred during treatment with 3 x 6.25 mg/day of captopril for 2 weeks was dry cough in 5 patients from group A (25%). In Group B, one patient complained of cough, but the patient also suffered from lung tuberculosis. Van Vliet found 1 out of 8 patients with similar complaints after administration of 18.75 mg/day of captopril for 3 months.[13] Confusion was found in 2 patients in group A (10%), pruritus in 2 patients (10%). Yorgensen found 2 patients with confusion out of 4 respondents. Whether confusion was a side effect of captopril, or whether it was caused by something else, was still uncertain.[17]

The systolic blood pressure of group A patients, who received 3 x 6.25 mg /day of captopril for 2 weeks, was significantly reduced ($p < 0.001$). Compared to group B, which was not given captopril, the systolic blood pressure did not undergo any significant change. Van Vliet found an average systolic drop from 104.0 ± 10.6 to 98.7 + 8.6 during administration of 18.75 mg / day of captopril for 11 – 14 days. According to Van Vliet, the patient's blood pressure should stabilize if the dose was reduced to 2 x 6.25 mg/day.[13] The patients' diastolic blood pres-

sure showed an insignificant drop. In general, the blood pressure was reduced, but low dose captopril does not cause hemodynamic imbalance.

The patients' bodyweight and abdominal circumference of the two groups both showed an insignificant reduction. Diuresis in those who received captopril was significantly increased, while those who did not receive captopril showed an insignificant increase. Natriuresis in those receiving captopril was also significantly increased, while those who did not receive captopril showed an insignificant increase. Van Vliet also found a significant increase in natriuresis after administration of captopril.[13] Addition of captopril in a diuretic regiment is known as the nephron blockage seies. Combination of loop diuretics and potassium-saving diuretics would prevent potassium reabsorption at the distal tubuli. Stimulation of the RAA system would increase sodium reabsorption along the proximal tubulus due to a high influence of angiotensin II. Administration of captopril reduces angiotensin II, thus decreasing sodium reabsorption and increasing natriuresis.[13]

The blood ureum level of Group A patients showed an insignificant increase. The blood ureum level of Group B patients increased significantly. Whether or not an increase in blood ureum level shows reduced renal function that decreases natriuresis is still unclear. The creatinine level of Group A patients showed a significant increase, while for Group B, the increase was insignificant. There was no significant change in blood potassium for both groups A and B. The blood sodium of patients from group A showed an insignificant increase, while those from group B showed an insignificant decrease. The same thing occurred in Van Vliet's study, where no significant changes in blood sodium and potassium levels were found after administration of captopril.[13] The average blood albumin for both groups A and B demonstrated an insignificant increase.

CONCLUSION

In this study, low dose captopril adjuvant in patients with liver cirrhosis and ascites who have received standard therapy:

1. Increased natriuresis and improved diuretic response.
2. Reduced systolic blood pressure without causing hemodynamic imbalance.
3. Reduced bodyweight and abdominal circumference, even though not significantly.
4. Did not cause significant changes in electrolyte levels.
5. Caused a side effect of cough in 25% of patients.

SUGGESTION

1. Further study with a larger sample is needed to achieve better results.
2. There needs to be longer serial evaluation.
3. Captopril may be used as an alternative adjuvant therapy in refractory ascites.

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