SUPPLEMENT

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High Dose Oral Furosemide with Salt Ingestion in the Treatment of Refractory Ascites of Liver Cirrhosis

Abstract

Purpose: We aimed to evaluate and compare the efficacy and safety of high-dose furosemide+salt orally by comparing HSS+ furosemide (i.v.) and repeated paracentesis in patients with RA.

Methods: This was a prospective study of 78 cirrhotic patients with RA, randomized into three groups: Group A (n= 25) i.v. furosemide (200-300 mg bid) and 3% hypotonic saline solution (HSS) (once or twice a day); Group B (n= 26) oral furosemide tablets (360-520 mg bid) and salt (2.5 g bid); and, Group C (n= 27) repeated large-volume-paracentesis (RLVP) with albumin infusion. Patients without hyperkalemia were administrated 100 mg of spironolactone/day. During the follow-up; INR, creatinine, and total bilirubin levels were measured to determine the change in MELD (model of end stage liver disease) score.

Results: Hepatic encephalopathy (HE), severe episodes of spontaneous bacterial peritonitis (SBP) and pleural effusions (PE) occurred more frequently in Group C. Improvement in Child-Pugh and MELD score was better in Group A and B than Group C. In Group B, improvements were seen in the Child-Pugh and MELD score, reduction in body weight, duration and number of hospitalization. In Groups A and B, remarkable increases in diuresis were observed (706 ± 116 to 2425 ± 633 mL and 691 ± 111 to 2405 ± 772 mL) and serum sodium levels also improved. HE and SBP were occurred more often in group C ($p < 0.002$). Hospitalization decreased significantly in Group B ($p < 0.001$). There was no significant difference in survival among groups.

Conclusion: High dose oral furosemide with salt ingestion may be an alternative, effective, safe and well-tolerated method of therapy for RA.

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Cirrhosis is a severe scarring of the liver and poor liver function seen at the terminal stages of chronic liver disease. Progression of chronic liver disease to liver cirrhosis varies and depends on the etiology and the patient. The main form of treatment is liver transplantation, but many patients with this complication receive palliative therapies, among which therapeutic paracentesis is the frequently used.

Decompensated cirrhosis has one or several of the following findings: ascites, esophageal varicose bleeding, hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), hepatocellular carcinoma, hepatorenal syndrome, hepatopulmonary syndrome and hypersplenism and hematological disorders [1, 2]. One of the most important findings is the presence of ascites - the accumulation of fluid in the pleural cavity and/or in the peritoneal cavity [3]. In patients with cirrhosis, ascites is defined as refractory when it can not be mobilized or recurs early in standard diuretic therapy. Refractory ascites (RA) is a critical and difficult-to-treat complication of advanced liver cirrhosis and 50% of such patients die within 6 months of its beginning [4, 5].

Technically, RA is defined as ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by lack of response to sodium-restricted diet and high-dose diuretic treatment (160 mg/day furosemide and 400 mg/day of spironolactone) or development of diuretic-induced complications to preclude using effective diuretic dosage [4]. The diuretic-induced complications include HE, serum creatinine levels more than 2 mg/dL, serum sodium level less than 125 mEq/L (hyponatremia) and serum potassium level less than 3 mEq/L or greater than 6 mEq/L and possible kidney failure [6].

For ascites grade II and III patients, the fluid accumulation in the peritoneal and/or pleural cavity can be controlled with salt restriction, bed rest and oral diuretic therapy. Daily sodium intake in the salt-free diet is kept below 200 mg [6, 7]. With bed rest, lying position eliminates increase of aldosterone secretion caused by postural changes. Diuretic treatment within a few weeks or may recurred ascites. For patients in this situation, there are a variety of therapeutic options that may been attempted: therapeutic repeated large-volume-paracentesis (PLVP) accompanied with intermittent i.v. albumin, transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation [8].

The prevalence and incidence of cirrhosis with RA are progressively increasing worldwide, and new medical strategies are needed for the treatment of patients. Recently, a new treatment approach has been developed: HSS (150 mL H₂O

with 1.4-4.6 % NaCl solution) with high-dose i.v. furosemide (250-1000 mg bid i.v.). According to the a case report, HSS leads to increased renal blood flow and reduced sympathetic tone, so it has the potential to be an effective treatment for RA [9].

The goal of this study was to evaluate the success and the reliability of treatment approach of salt orally+high-dose diuretics. Our evaluation criteria are a reduction in body weight, improvement of Child-Pugh and MELD (model of end stage liver disease) score, decrease in duration of hospital stay and number of hospitalization, decrease in serum sodium levels and improvement in any-coexisting fluid and HE.

Materials and Methods

Patients

Seventy eight (47 male and 31 female, 35-85 years) cirrhotic patients with RA who had been admitted to the Gastroenterology units of Baskent University Hospital in Adana and the Gastroenterology units of Mustafa Kemal University Medical Faculty in Hatay, Turkey; between January 2012 and November 2015, were studied retrospectively. Enrollment in the study was offered to them after the diagnosis of RA. All patients were evaluated with clinical examination, routine hematological, biochemical, serological investigations and abdominal USG.

Eligibility criteria

Diagnosis was based on the following diagnostic criteria for RA which was defined by the IAC criteria1 [10] as one of the following:

- (a) Diuretic-resistant RA: <1.5 kg/week weight loss while being treated with furosemide (160 mg/day) and spironolactone (400 mg/day) or an equivalent dose of a loop-acting and distal-acting diuretic;
- (b) Diuretic-intractable RA: <1.5 kg/week weight loss as a result of the inability to use an effective dose of diuretic because of development of diuretic-induced hyponatremia (sodium level <125 mEq/L), hyperkalemia (potassium level >5.5 mEq/L), renal failure (doubling of serum creatinine level >2.5 g/dL) or encephalopathy; or,
- (c) Previous dietary restriction of sodium between 50 and 66 mEq/day.

Patients had been identified as diuretic-resistant ascites (patient's ascites cannot be controlled despite salt restriction+maximal dose of diuretic therapy) and diuretic-intractable ascites (patients were unable to use effective doses of diuretics because of side effects of diuretic).

These patients were randomly assigned to Groups A, B or C. Patients who took high doses of furosemide therapy must have hyponatremia (serum sodium level <130 mEq/L), according to the defined criterion above.

Exclusion criteria were congestive heart failure, renal failure, complete portal vein thrombosis, nonsteroidal anti-inflammatory medications, active infection, hepatocellular carcinoma and other malignancies. The first furosemide and salt treatment was administered under observation at the hospital. Ascites assessment was analyzed with IAC criteria as one of three stages (Stage I: only detectable with USG; Stage II: moderate ascites with symmetrical distension of the abdomen; Stage III: Marked or tensor ascites, with marked distension). Treatment plans for basal evaluations in the first 24 hours were not implemented.

Study Design

Group A: Spironolactone tablets (1x100 mg/day fixed dose) and i.v. infusion of furosemide (2x240 mg/day) (speed not exceeding 4 mg/min) was applied. If reduction of daily weight was less than 500 g, dose increased 2x300 mg on the 2nd day and if there was still not the desired weight loss, then dose increased 2x360 mg on the 3rd. After sufficient diuresis level has been captured, the patient was kept in the hospital until ascites evidence (Phase II) had clinically disappeared. HSS: 150 ml of 3% NaCl was given as a single dose by infusion over 30 min the morning of the day in which furosemide was given.

Group B: On the 1st day, spironolactone tablet 1x100 mg/day fixed dose and furosemide tablet 2x360 mg dose were administered. If the reduction of daily weight was less than 500 g, on 2nd day 2x440 mg dose was administered. If desired weight loss had still not been reached, on 3rd day 2x520 mg dose increases were administered. After sufficient diuresis level had been realized, the patient was kept in the hospital until ascites evidence (Phase II) clinically disappeared. Oral Salt: Added into a glass of unsalted buttermilk setting as morning and evening 2x3 gr the day on which high-dose furosemide was given.

Group C: All ascites was poured at once during total RLVP application. As support, 6 g albumin solutions were given per liter of the discharged ascites.

Follow-up Period: After discharge from the hospital, patients were observed as outpatients once biweekly for 2 months, then monthly for 14 months.

Sample Collection and Laboratory Analysis

Venous blood from all study subjects was collected in EDTA-containing and no-additives-containing tubes. The plasma and serum were separated by low-speed centrifugation (4°C, 1200 g and 10 minutes). Grossly hemolyzed or lipemic specimens were not used. Serum levels of bilirubin, creatinine, sodium, potassium, uric acid and albumin and urine levels of sodium and potassium were measured in an Abbott AEROSET autoanalyzer using Abbott kits (Abbott Laboratories, Abbott Park, IL, USA).

Prothrombin time (PT) was measured using a Coagumaster (Hitachi, Tokyo, Japan) and Simplastin Automated (Lot no. 100313, ISI= 2.16, Organon Teknika, Durham, NC, USA) as the reagent. PT-INR was calculated by the formula: PT-INR= (PT seconds of patient's plasma/PT seconds of normal control).

All patients were tested for viral hepatitis (HBV and HCV). Chest X-rays were taken in patients with pleural effusion. Daily performed follow-ups included weight, urine output and supine waist circumference (WC). Arterial blood pressure and pulse rate are measured bid. After the start of treatment (on 3rd and 6th days at the hospital and 14th day), serum and urine creatinine and sodium and potassium levels were analyzed.

After the initial outpatient assessment, use of oral salt and oral diuretics were continued at home at the level of dose previously administered, when body weight and WC increased.

Predicted undesirable side effects related to applications

I.v. high-dose infusion of furosemide was more common, particularly in clinical cardiology procedure. Undesirable side effects generally involved fluid and electrolyte loss, which can be checked during the hospitalization. Since oral high-dose diuretic was calculated close to i.v. dose, it had similar side effects profile that could be controlled.

- Efficacy endpoints were as follows:
- reduction in body weight at discharge;
- relief of overt ascites at discharge 3 days after the end of diuretic treatment period (orally or i.v.) or after the last RLVP (ascites graded according to IAC criteria) ;
- improvement in Child Pugh score at discharge;
- improvement of MELD score at discharge;
- decline in hospital stay and hospitalization;
- improvement in any co-existing fluid overload (pretibial edema, PE),

- improvement in HE, and,
- decline in incidence of SBP.

This study was approved by Hatay Mustafa Kemal University Medical Faculty institutional review board and ethics committee. The written informed consent, in accordance with the Helsinki Declaration was obtained from all participants at inclusion.

Statistical Analysis

All parametric results are expressed as mean±standard deviation (SD). The SPSS statistical software package (SPSS, version 20 for Windows; SPSS Inc., Chicago, Illinois, USA) was used to perform all statistical calculations. Variables were

evaluated by using the non-parametric Mann-Whitney U test for statistical analysis. Categorical variables were compared with the X² test. Comparisons between the groups were done using Student's t-test or Mann-Whitney U test as appropriate. The Wilcoxon signed-rank test was used for the comparison of continuous data. The correlation between variables was evaluated by Fisher's Exact Test and Continuity correction as appropriate. All tests of significance were two-sided, and $p < 0.05$ were considered statistically significant.

Results

We recruited 78 patients with RA (47 with diuretic-resistant RA and 31 with diuretic-intractable RA). All patients agreed

TABLE 1: Clinical and laboratory variables of Group A, B and C before and after treatment

	Patient Groups								
	Furosemide+HSS Group A			High-dose Furosemide+Salt Orally Group B			Paracentesis Group C		
	Before	After	P	Before	After	P	Before	After	P
Number of subjects	25			26			27		
Weight (kg)	77.84±7.90	73.60±7.15	<0.001	75.50±6.91	70.88±6.16	<0.001	76.33±10.10	75.26±9.92	0.010
Diuresis (mL/day)	676.60±99.7	2103.20±581.88	<0.001	585.23±101.52	1702.31±356.41	<0.001	654.07±53.8	681.85±83.53	0.060
Bilirubin (mg/dL)	1.90±0.43	2.01±0.76	0.919	1.75±0.4	1.82±0.53	0.236	2.10±0.43	2.37±0.54	<0.001
Serum sodium (mEq/L)	126.52±2.65	131.04±2.42	<0.001	125.69±2.43	130.31±2.31	<0.001	128.07±3.49	126.30±4.09	<0.001
Serum potassium (mEq/L)	4.99±0.73	4.30±0.66	0.006	4.40±0.60	4.17±0.75	0.236	4.69±0.50	5.20±0.59	0.004
Serum creatinin (mg/dL)	1.81±0.49	1.44±0.39	0.001	1.36±0.21	1.42±0.44	0.925	1.39±0.28	2.21±0.66	<0.001
Uric acid (mg/dL)	6.20±0.67	8.10±1.25	<0.001	6.31±0.50	8.06±0.78	<0.001	6.40±0.65	7.51±1.02	<0.001
Urinary sodium (mEq/24h)	34.16±17.47	90.48±26.65	<0.001	35.35±14.60	78.04±26.47	<0.001	32.22±13.31	33.15±15.21	0.258
Urinary potassium (mEq/24h)	44.13±10.33	48.42±15.29	0.277	49.31±14.52	44.35±14.34	0.195	40.72±12.17	42.64±15.11	0.565
PT (% of control)	41.44±15.76	35.76±15.04	0.028	56.69±16.41	47.46±14.81	0.001	35.30±15.75	28.96±13.59	0.001
INR	1.71±0.23	1.79±0.35	0.673	1.62±0.21	1.65±0.25	0.443	1.91±0.33	2.17±0.51	<0.001
PE, <i>n</i> (%)	7 (28%)	2 (8%)	0.063	3 (11.5%)	2 (7.6%)	1.00	1 (3.7%)	3 (11.1%)	0.500
HE, <i>n</i> (%)	1 (4%)	1 (4%)	1.00	-	6 (23.1%)	0.63	2 (7.4%)	16 (59.3%)	<0.001
SBP, <i>n</i> (%)	1 (4%)	2 (8%)	1.00	2 (7.7%)	2 (7.7%)	1.00	4 (14.8%)	13 (48.1%)	0.004
MELD Score	11.24±4.53	13.44±8.58	0.045	8.50±2.73	10.08±6.95	0.189	14.22±4.75	19.22±8.95	0.00
Modified MELD score	19.76±3.91	17.04±6.53	0.017	18.77±2.16	14.69±6.05	0.003	21.704±4.34	23.26±7.94	0.068
Child-Plug score	10.52±1.48	9.04±2.48	<0.001	9.81±1.36	8.58±1.98	0.001	11.33±1.18	12.30±1.75	<0.001

Variables are expressed as mean±SD

TABLE 2: Results of RA patients after the treatments

	Furosemide +HSS Group A	High-dose Furosemide +Salt Orally Group B	Seriate Paracentesis Group C
Number of subjects	25	26	27
Ascites grade, <i>n</i> (%)			
0	1 (4%)	8 (30.7%)	-
I	16 (64%)	10 (38.4%)	5 (18.5%)
II	7 (28%)	7 (26.9%)	21 (77.7%)
III	1 (4%)	1 (3.8%)	1 (3.7%)
Pretibial edema, <i>n</i> (%)			
0	18 (72%)	16 (61.5%)	13 (48.1%)
I	7 (28%)	8 (30.7%)	8 (29.6%)
II	-	1 (3.8%)	5 (18.5%)
III	-	-	1 (3.7%)
Acute renal failure, <i>n</i> (%)	2 (8%)	3 (11.5%)	10 (37%)
Hepatorenal sendrom, <i>n</i> (%)	-	2 (7.7%)	4 (14.8%)
GI bleeding, <i>n</i> (%)	4 (16%)	4 (15.4%)	10 (37%)
Hospitalization number	14.20±4.86	10.65±8.58	21.96±6.64
Hospital stay (day)	3.88±0.83	2.85±0.78	1.89±1.34
Follow-up period (month)	14.24±2.91	14.38±4.63	13.56±2.31
Survival time (month)	15.4±3.18	15.5±4.54	13.39±2.62
Deaths, <i>n</i> (%)	6 (24%)	4 (15.4%)	12 (44.4%)
Hospital deaths, <i>n</i> (%)	5 (20%)	2 (7.7%)	9 (33.3%)

Variables are expressed as mean±SD.

to participate in the study and were randomized into three groups: 25 were assigned to Group A, 26 to Group B and 27 Group C. Participants had no history of exposure to toxins or usage of other drug.

Laboratory and clinical parameters

As shown in Table 1, before the treatment, natriuresis was low in most patients, despite their receiving high dose oral furosemide or combinations of diuretics. Highest diuresis was seen in Group A (676.60±99.7 mL/day) and lowest diuresis was in Group B (585.23±101.52 mL/day). Serum albumin level means were higher than 2.80 g/L in all groups. Symptoms and clinical parameters, dyspnea, lower-limb edema, fatigue or

TABLE 3: Comparison between the two groups treated with furosemide+HSS (Group A) and with high-dose furosemide+salt orally (Group B)

	Furosemide+HS S Group A	High-dose Furosemide+Salt Orally Group B	P
Number of subjects	25	26	
Diuresis (mL/day)	2103.20±581.88	1702.31±356.41	0.001
Serum creatinin (mg/dL)	1.44±0.39	1.42±0.44	0.827
Serum sodium(mEq/L)	131.04±2.42	130.31±2.31	0.246
Serum potassium (mEq/L)	4.30±0.66	4.17±0.75	0.383
Urinary sodium (mEq/24 h)	90.48±26.65	78.04±26.47	0.115
Urinary potassium (mEq/24 h)	48.42±15.29	44.35±14.34	0.246
Urinary acid (mg/dL)	8.11±1.25	8.06±0.78	0.920
PT (% of control)	35.76±15.04	47.46±14.81	0.008
PE, <i>n</i> (%)	2 (8%)	2 (7.7%)	1.00*
HE, <i>n</i> (%)	1 (4%)	6 (24.1%)	0.099*
SBP, <i>n</i> (%)	2 (8%)	2 (7.7%)	1.00*
Child Pugh score	9.04±2.48	8.58±1.98	0.446
MELD score	13.44±8.58	10.08±6.95	0.034
Modified MELD score	17.04±6.53	14.69±6.05	0.102
Acute renal failure, <i>n</i> (%)	2 (8%)	3 (11.5%)	1.00*
Hepatorenal sendrom, <i>n</i> (%)	-	2 (7.7%)	0.49
GI bleeding, <i>n</i> (%)	4 (16%)	4 (15.4%)	1.00
Hospitalization number	14.20±4.86	10.65±8.58	0.001
Hospital stay (day)	3.88±0.83	2.85±0.78	<0.001
Follow-up period (month)	14.24±2.91	14.38±4.63	0.951
Survival time (month)	15.4±3.18	15.5±4.54	0.698
Deaths, <i>n</i> (%)	6 (24%)	4 (15.4%)	0.337*
Hospital deaths, <i>n</i> (%)	5 (20%)	2 (7.7%)	0.248*

Variables are expressed as mean±SD. * results of Fisher's Exact Test, ** Contunuity Correction

TABLE 4: Comparison between with high-dose furosemide+salt orally (Group B) and with paracentesis (Group C)

	High-dose Furosemide+Salt Orally Group B	Paracentesis Group C	P
Number of subjects	26	27	
Diuresis (mL/day)	1702.31±356.41	681.85±83.53	<0.001
Serum creatinin (mg/dL)	1.42±0.44	2.21±0.66	<0.001
Serum sodium (mEq/L)	130.31±2.31	126.30±4.09	<0.001
Serum potassium (mEq/L)	4.17±0.75	5.20±0.59	<0.001
Urinary sodium (mEq/24 h)	78.04±26.47	33.15±15.21	<0.001
Urinary potassium (mEq/24 h)	44.35±14.34	42.64±15.11	0.546
Urinary acid (mg/dL)	8.06±0.78	7.51±1.02	0.077
PT (% of control)	47.46±14.81	28.96±13.59	<0.001
PE, <i>n</i> (%)	2 (8%)	3 (11%)	1.00*
HE, <i>n</i> (%)	6 (23%)	16 (59%)	0.017**
SBP, <i>n</i> (%)	2 (7.7%)	13 (48%)	0.002*
Child Pugh score	8.58±1.98	12.30±1.75	<0.001
MELD score	10.08±6.95	19.22±8.95	<0.001
Modified MELD score	14.69±6.05	23.26±7.94	<0.001
Acute renal failure, <i>n</i> (%)	3 (11.5%)	10 (37%)	0.049*
Hepatorenal sendrom, <i>n</i> (%)	2 (7.7%)	4 (14.8%)	0.669
GI bleeding, <i>n</i> (%)	4 (15.4%)	10 (37%)	0.119
Hospitalization number	10.65±8.58	21.96±6.64	<0.001
Hospital stay (day)	2.85±0.78	1.89±1.34	<0.001
Follow-up period (month)	14.38±4.63	13.56±2.31	0.519
Survival time (month)	15.5±4.54	13.39±2.62	0.196
Deaths, <i>n</i> (%)	4 (15.4%)	12 (44.4%)	0.035*
Hospital deaths, <i>n</i> (%)	2 (7.7%)	9 (33.3%)	0.039*

Variables are expressed as mean±SD. * results of Fisher's exact test, ** Contunuty Correction

weakness, were observed in all participants.

As shown in Table 1, after the treatment, a significant increase was observed in daily diuresis in Groups A and B ($p < 0.001$ for both Groups A and B). Daily sodium output increased in Group A and B, with a significant difference for both ($p < 0.001$). Serum sodium and uric ascites levels increased significantly ($p < 0.001$ for both Groups A and B) and body weight increased significantly in all groups ($p < 0.001$ for both Groups A and B; $p = 0.010$ for Group C). Serum bilirubin level and INR increased significantly in Group C ($p < 0.001$ for both metabolites). Urinary sodium levels were significantly increased which could represent an improvement of diuretic response in patients of Group A and B ($p < 0.001$ for both).

In Group B, the changes in MELD and Child-Pugh scores were significantly higher ($p < 0.001$) than those seen in Group C. There was a significant difference in the degree of improvement of the MELD score between Groups A and B ($p = 0.034$) (as seen in Table 3 and 4).

Hepatic-encephalopathy

During the follow-up period, 4% of patients in Group A, 23.1% in Group B and 59.3% in Group C experienced one or more episodes of HE (Table 1). In Group C, the total number of episodes of encephalopathy was significantly greater than during follow-up period ($p = 0.001$).

Gastrointestinal-bleeding (GI)

During the follow-up period, 16% of patients from Group A, 15.4% from Group B, and 37% from Group C experienced an episode of GI bleeding (Table 2); the differences were not statistically significant in Group C when compared individually to Group B ($p = 0.119$). The source of bleeding was esophageal varices in all patients.

Spontaneous bacterial peritonitis

During the follow-up period, 8% of patients from Group A, 7.7% from Group B and 48.1% from Group C experienced an episode of SBP (Table 1); the episodes were significantly more frequent in Group C than group B ($p = 0.002$). Also, during the follow-up period, there was a significant increase in number of SBP patients in Group C ($p = 0.004$).

Hospitalization Number and Hospital Stay

Group B hospitalization number (10.65 ± 8.58) was significantly lower than ($p = 0.00$) Group A (14.20 ± 4.86) and

Group C (21.96 ± 6.64) hospitalization (Table 3 and 4). Also, hospital stay (as day) was lowest in Group B when compared individually with the other two groups ($p = 0.00$).

Survival

As seen in Table 2, six patients in Group A (24%) died during the follow-up period (12-20 months); three patients died of GI, one of pneumonia, one of SBP and one of sepsis. Four patients in group B (15.4%) died - that was the lowest mortality rate among all groups and during the follow-up period (6-30 months); two patients died of GI, one of sepsis and one of hepatorenal syndrome. Group C had the highest mortality rate, with 12 patient deaths (44.4%) including nine patients (33.3%) who died while still in the hospital. The main cause of death in the RLVP group was hepatorenal syndrome (41.6% of deaths).

Other Results

The most severe pretibial edema, level (III), was mostly observed in Group B (30.7%). There was no significant difference among groups in INR before the trial. Acute renal failure and hepatorenal syndrome were more in Group C among all other groups (as seen in Tables 2).

Discussion

RA is defined by the lack of response to a low sodium diet and diuretics or occurrence of serious diuretic induced complications [9]. In other words, RA may not be mobilized or early reappearance after treatment and may not be prevented by medical therapies. Several different therapeutic approaches have been tested in cirrhotic patients with RA; including, surgical portocaval anastomosis [11], paracentesis with i.v. albumin infusion [12], transjugular intrahepatic portocaval shunt [12] and diuretics [13].

Cirrhotic patients with RA are characterized by renal sodium and water retention with edema formation. Abnormalities influence renal function that antagonized diuretics effects. Mobilization of extra vascular fluid through the osmotic action of HSS and rapid excretion of the volume by the support of diuretics is the most often used treatments of cirrhosis. HSS is based on the quick elevation of NaCl concentration with increased osmotic pressure, volume mobilization into vascular compartment and increasing in renal blood flow that stimulates renal perfusion. Spironolactone and loop diuretics were associated with HSS to get success. The effective dosage of diuretics resulted in increasing of renin activity and also serum aldosterone level.

Aldosterone regulates blood pressure and increases reabsorption of ions and water in the kidney to cause the conservation of sodium, secretion of potassium, increase in water retention, blood pressure, and blood volume. HSS can increase the efficiency of diuretic treatment by expanding arterial circulation volume and increasing distribution of the sodium.

Generally, paracentesis is the first choice treatment of RA. Few studies have compared paracentesis *versus* diuretics+HSS. Quintero *et al.* [14] studied with randomly-assigned patients to treatment with either paracentesis+i.v. albumin infusion or diuretics, showing similar outcomes between two groups. Salerno *et al.* [15] stated that repeated paracentesis with human albumin replacement was safe, effective and more rapid than traditional diuretic therapy in treating tense ascites. These studies hypothesized that some diuretics may also impair the urea cycle leading to decreased hepatic transformation of ammonia to urea. There are some disadvantages of repeated paracentesis: early phase healing was rapidly followed by post-paracentesis HE, GI bleeding and SBP [16], which are the main reasons of death in RA. In the present study, we found that HE ($p = 0.017$) and SBP ($p = 0.002$) were significantly better in Group B compared with Groups C (Table 4). According to the results, the relative risk of GI was 2.4 times greater in Group C patients, compared with Group B patients. Comparison between Groups B and C showed that diuretics+oral salt also provided a clinical benefit; patients treated with diuretics+oral salt had a significantly better survival and lower morbidity than patients treated with RLVP.

Another factor which contributes to the improvement in survival reduces the morbidity of patients treated with diuretics+ salt used orally might have been the noticeable reduction in the number of RLVP intervention during the treatment period. Even if RLVP procedures are combined with an albumin infusion, it carries a risk of post-paracentesis circulatory dysfunction complication that causes reduces long-term survival [3, 17]. These RLVP risks should be eliminated to improve patient survival. Alternative RA treatment methods like post-paracentesis parenteral-nutritional-support with a balanced oral diet and an evening protein snack are not sufficient to reduce HE, SBP and GI bleedings [18].

On the other hand, recent studies support the effectiveness of alternative diuretics. Preliminary studies have tested the safety and tolerability of HSS and furosemide combination [19], and suggest that combination therapy is preferred instead of treatment with furosemide alone [20]. In patients with RA, ascites level, PE, and leg edema were

significantly better in patients treated with high-dose furosemide+HSS [13]. Side effects of the treatment can be managed with suggested strategies [13]. This method has been quite effective for congestive heart failure (CHF) associated with compensated cirrhosis [21]. Licata *et al.* demonstrated, in their work with RA, that CHF patients that administration of i.v. furosemide and HSS is a safe and effective treatment [9, 22]. The preliminary study in 2003 showed that the group with HSS treatment in combination with furosemide responded better to diuresis and natriuresis due to the increased sodium. By the end of the year, the mortality rate declined from 55% to 13% [22]. In 2009, the same research team implemented HSS treatment with high-dose furosemide to 60 of 84 patients with RA [8]. In that pilot study, there has been a significant increase in diuresis ($p < 0.001$), improvement in Child-plug score ($p = 0.004$), considerable decline in the ascites at discharge ($p < 0.001$) and pretibial edema ($p < 0.001$). On the other hand, there was no statistically significant reduction in GI bleedings ($p = 0.07$), hospitalization days ($p = 0.68$) or HE ($p = 0.67$). HE was as a result of plasma volume expander through osmotic effect of observed high efficacy sodium chloride. It has been showed that diuretics+HSS treatment was generally more reliable and effective alternative than RLVP, but there was no significant reduction in hospitalization stay (9.4 ± 2.2 days) [9]. In the present study, compared with the furosemide+HSS group, patients with high-dose furosemide+salt orally group had significantly better values for hospitalization number ($p = 0.001$) and hospital stay ($p < 0.001$).

In conclusion, we evaluated the efficacy and safety of high-dose furosemide+salt orally with HSS+furosemide (i.v.) and repeated paracentesis with RA. High-dose furosemide+salt orally treatment method seems possible and practical. So, it should be considered as an alternative treatment – leading to improvement in HE, decline in the incidence of SBP and GI bleeding, improvement in MELD and Child-Pugh scores, decline in hospital stay and hospitalization duration, and prolong the lives of RA patients.

Limitations of the Study

Nevertheless, further studies are needed to confirm our findings and proceed and evaluate the limitations of treatments. Some limitations of the prospective study must be taken into account. First, our study was carried out with a relatively few patients. Ideally, it should be repeated with more patients in each group. Second, the follow-up period should be longer to evaluate long-term success of treatments.

References

1. Benvegna L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004; 53 (4); 744-9.
2. Gines P, Arroyo V, Quintero E, Planas R, Bory F, Cabrera J, Rimola A, Viver J, Camps J, Jimenez W. Et al. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. *Gastroenterology* 1987; 93 (2):234-241.
3. Çakaloğlu Y. Asit etiopatogenezi, tanı ve klinik özellikler. Ökten A (editör). *Klinik Pratikte Asitli Hasta*. 1. Baskı. İstanbul: İstanbul Medikal Yayıncılık, 2005; 7-36.
4. Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, Angeli P, Porayko M, Moreau R, Garcia-Tsao G, Jimenez W, Planas R, Arroyo V. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003; 38: 258-66.
5. Sonsuz A. Karaciğer sirozunda hasta takibi ve klinik sorunlar. Dobrucalı A, Tetikkurt C (editörler). *Türkiye'de Sık Karşılaşılan Hastalıklar II. Sindirim Sistemi Hastalıkları, Akciğer Kanseri Güncel Yaklaşım Sempozyum Dizisi No: 58*. İstanbul: Cerrahpaşa Tıp Fakültesi Yayınları, 2007; 99-112.
6. Sonsuz A. Karaciğer Sirozunda Hasta Takibi ve Klinik Sorunlar. İ.Ü. Cerrahpaşa Tıp Fakültesi Sürekli Tıp Etkinlikleri Sempozyum Dizisi, Kasım 2007; 58:99-112.
7. Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Schölmerich J. Definition and Diagnostic Criteria of Refractory Ascites and Hepatorenal Syndrome in Cirrhosis. *Hepatology* 1996; 23 (1):164-176.
8. Salerno F, Merli M, Riggio O, Cazzaniga M, Valeriano V, Pozzi M, Nicolini A, Salvatori F. Randomized Controlled Study of TIPS versus Paracentesis Plus Albumin in Cirrhosis with Severe Ascites. *Hepatology* 2004; 40: 629-635.
9. Licata G, Tuttolomondo A, Licata A, Parrinello G, Raimondos DD, Sciacca RD, Camma C, Craxi A, Paterna S, Pintos A. Clinical Trial: High-dose furosemide plus small-volume hypertonic saline solution vs. repeated paracentesis as treatment of refractory ascites. *Aliment Pharmacol Ther* 2009; 30 (3):227-235.
10. Arroyo V, Moreau R, Jalan R, Gines P, EASL-CLIF Consortium CANONIC Study. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. *J Hepatol*. 2015; 62: 131-43.
11. Franco D, Vons C, Traynor O, de Smadja C. Should portosystemic shunt be reconsidered in the treatment of intractable ascites cirrhosis? *Arch Surg* 1988; 123:987-991.
12. Elsabaawy MM, Aldelhamid SR, Alsebaey A, Abdelsamee E, Obada MA, Salman TA, Rewisha E. The impact of paracentesis flow rate in patients with liver cirrhosis on the development of

- paracentesis induced circulatory dysfunction. *Clin Mol Hepatol* 2015; 21(4):365-71.
13. Tuttolomondo A, Pinto A, Parrinello G, Licata G. Intravenous High-Dose Furosemide and Hypertonic Saline Solutions for Refractory Heart Failure and Ascites. *Seminars in Nephrology* 2011; 31: 513-522.
 14. Quintero E, Gines P, Arroyo V, Rimola A, Bory F, Planas R, Viver J, Cabrera J, Rodes J. Paracentesis versus diuretics in the treatment of cirrhotics with tense ascites. *Lancet* 1985;16 (8429): 611–2.
 15. Salerno F, Badalamenti S, Incerti P, Tempeni S, Restelli B, Bruno S, Bellati G, Roffi L. Repeated paracentesis and i.v. albumin infusion to treat ‘tense’ ascites in cirrhotic patients. A safe alternative therapy. *J Hepatol* 1987;5: 102–8.
 16. Pozzi M, Osculati G, Boari G, Boari G, Serboli P, Colombo P, Lambrughi C, De Ceglie S, Roffi L, Piperno A, Cusa EN, et al. Time course of circulatory and humoral effects of rapid total paracentesis in cirrhotic patients with tense, refractory ascites. *Gastroenterology* 1994; 106: 709-19.
 17. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. United Network for Organ Sharing Liver Disease Severity Score Committee. *Gastroenterology* 2003; 124(1):91-6.
 18. Schepke M, Roth F, Fimmers R, Brensing KA, Sudhop T, Schild HH, Sauerbruch T. Comparison of MELD, Child–Pugh, and emory model for the prediction of survival in patients undergoing transjugular intrahepatic portosystemic shunting. *Am J Gastroenterology* 2003; 98 (5):1167–1174.
 19. Paterna S, Parrinello G, Amato P, Dominquez L, Pinto A, Maniscalchi T, Cardinale A, Licata A, Amato V, Licata G, Di Pasquale P. Tolerability and efficacy of high-dose furosemide and small-volume hypertonic saline solution in refractory congestive heart failure. *Adv Ther* 1999;16 (5):219-28.
 20. Santos J, Planas R, Pardo A, Durandez R, Cabre E, Morillas RM, Granada ML, Jimenez JA, Quinetto E, Gassull MA. 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 (2):187-92.
 21. Cody RJ. Diuretics in the management of congestive heart failure. *Cardiologia* 1998; 43 (1): 25–34.
 22. Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, Argano C, Tuttolomonda A, Paterna S. Effects of high dose furosemide and smallvolume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long term effects. *Am Heart Journal* 2003; 145: 459–66.