Alimentary Pharmacology & Therapeutics

Clinical Trial: High-dose furosemide plus small-volume hypertonic saline solutions vs. repeated paracentesis as treatment of refractory ascites

G. LICATA*,[1], A. TUTTOLOMONDO*,[1], A. LICATA¶, G. PARRINELLO*, D. DI RAIMONDO§, R. DI SCIACCA*, C. CAMMÀ¶, A. CRAXÌ¶, S. PATERNA‡ & A. PINTO§

*Unità Operativa di Medicina Interna e Cardio-Angiologia, Dipartimento Biomedico di Medicina Interna e Specialistica, Di.Bi.M.I.S, University of Palermo, Palermo, Italy; ¶Unità Operativa di Gastroenterologia, Dipartimento Biomedico di Medicina Interna e Specialistica, Di.Bi.M.I.S, University of Palermo, Palermo, Italy; ‡Unità Operativa di Medicina D'Urgenza, Dipartimento Biomedico di Medicina Interna e Specialistica, Di.Bi.M.I.S, University of Palermo, Palermo, Italy; §Unità Operativa di Fisiopatogia Circolatoria, Dipartimento Biomedico di Medicina Interna e Specialistica, Di.Bi.M.I.S, University of Palermo, Palermo, Italy

Correspondence to:
Dr A. Tuttolomondo, Cattedra di Medicina Interna, Di.Bi.M.I.S., P.zza delle Cliniche n. 2, 90127 Palermo (Italy).
E-mail: brunotutto@unipa.it

[1]These authors contributed equally to the article.

Publication data
Submitted 10 February 2009
First decision 1 March 2009
Resubmitted 5 May 2009
Accepted 7 May 2009
Epub Accepted Article 12 May 2009

SUMMARY

Background
In patients with cirrhosis, ascites is defined as refractory when it cannot be mobilized or recurs early in standard diuretic therapy.

Aim
To compare the safety and efficacy of intravenous high-dose furosemide + hypertonic saline solutions (HSS) with repeated paracentesis in patients with cirrhosis and refractory ascites.

Patients and methods
Eighty-four subjects (59/25 M/F) with cirrhosis, mostly of viral aetiology, admitted for refractory ascites, were randomly assigned to receive furosemide (250–1000 mg/bid i.v.) plus HSS (150 mL H_2O with NaCl 1.4–4.6% or 239–187 mEq/L) (60 patients, Group A) or to repeated paracentesis and a standard diuretic schedule (24 patients, Group B).

Results
During hospitalization, Group A patients had more diuresis (1605 ± 131 mL vs. 532 ± 124 mL than Group B patients; $P < 0.001$) and a greater loss of weight at discharge (−8.8 ± 4.8 kg vs. −4.5 ± 3.8 kg, $P < 0.00$). Control of ascites, pleural effusions and/or leg oedema was deemed significantly better in Group A.

Conclusions
This randomized pilot study suggests that HHS plus high-dose furosemide is a safe and effective alternative to repeated paracentesis when treating hospitalized patients with cirrhosis and refractory ascites. Larger studies will be needed to evaluate long-term outcomes such as readmission and mortality.

doi:10.1111/j.1365-2036.2009.04040.x

INTRODUCTION

According to the International Ascites Club,[1] refractory ascites is defined by the lack of response to high doses of diuretics (spironolactone 400 mg/day and furosemide 160 mg/day) or the development of adverse effects (hyperkalemia, hyponatremia, hepatic encephalopathy or renal failure) that prohibit further use of diuretics. Few studies have compared paracentesis and diuretics in the treatment of tense or refractory ascites. Quintero *et al.*[2] randomly assigned patients with tense ascites to treatment with either paracentesis plus intravenous albumin infusion or diuretics, showing similar outcomes. Salerno *et al.*[3] confirmed that repeated paracentesis with human albumin replacement was safe, effective and more rapid than traditional diuretic therapy in treating tense ascites. Paracentesis poses, however, a number of issues in patient management and alternative treatments to overcome the limitations of diuretic therapy and repeated paracenteses are certainly needed.[4, 5]

Cirrhosis and congestive heart failure (CHF) are major clinical disease states characterized by renal sodium and water retention with oedema formation. In these diseases, abnormalities of circulatory and volume homeostasis elicit neuro-hormonal responses influencing renal function and leading to retention of sodium and water.[6] Furthermore, prior observations in human subjects and in experimental animals with either cirrhosis[7–10] or CHF indicate that an increase in efferent renal sympathetic nerve activity (ERSNA), which served to antagonize the diuretic and natriuretic effects of atrial natriuretic peptides, is present and contributes to the renal sodium and water retention.

The model of refractory congestive heart failure, on the basis of these similarities and taking into account other pathophysiological differences between these two syndromes, may be helpful when exploring possible innovative treatments for refractory ascites in cirrhosis.

When diuretic resistance occurs in CHF, proposed therapeutic options include higher doses of furosemide or constant furosemide infusion.[11] Several studies have demonstrated the efficacy of hypertonic saline solution (HSS) infusion when regional organ blood flow is impaired.[12] HSS was first applied in this way for the primary treatment of severe haemorrhagic and traumatic shock and this therapy promptly restored central hemodynamics and peripheral blood flow.[12] The suggested mechanisms were direct myocardial stimulation with high cardiac output maintenance,[12, 13] increase in intravascular volume,[14] reduction in tissue oedema (shifting of tissue water along the osmotic gradient), increased renal blood flow and reduced sympathetic tone.[15] All of these mechanisms are potentially relevant to the treatment of refractory ascites in cirrhosis.

A few years ago, our group performed a randomized study[16] to evaluate the effects of the combination of high-dose furosemide and small-volume HSS in the treatment of refractory CHF. One hundred seven patients with refractory CHF were randomized to receive an IV infusion of furosemide (500–1000 mg) plus HSS (150 mL of 1.4–4.6% NACl) in 30 min twice a day or furosemide alone (500–1000 mg) twice a day over 6 to 12 days, on a normosodic diet. A significant increase in daily diuresis and natriuresis was observed in both groups, but it was more significant in the group receiving HSS, in which the serum Na level also increased. High-dose furosemide plus HSS was effective and well-tolerated, leading to improvement in the quality of life measurements of CHF. It also reduced mortality after discharge (survival 55% vs. 13% at 1 year).

On the basis of our former experience,[16] we have designed a study aiming to evaluate the safety and efficacy of intravenous high-dose furosemide plus HSS compared with repeated paracentesis and a standard oral diuretic schedule, in patients with cirrhosis and refractory ascites.

PATIENTS AND METHODS

All consecutive cirrhotic patients presenting between January 2002 and December 2007 with refractory ascites unresponsive to ambulatory treatment at Palermo's University Hospital (Azienda Ospedaliera Policlinico 'Paolo Giaccone') who were admitted to two Units (Internal Medicine; Emergency Medicine) of the 'Dipartimento Biomedico di Medicina Interna e Specialistica' of University of Palermo were offered enrolment in the study protocol after a diagnosis of refractory ascites had been made and all potential contraindications excluded.

Refractory ascites was defined according to the International Ascites Club criteria[1] as either: (a) diuretic-resistant refractory ascites: <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; or (b) diuretic-intractable refractory ascites: <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 or values >2.5 g/dL) or encephalopathy; (c) previous dietary restriction of sodium between 50 and 66 mEq/day.

The ascites was considered symptomatic if it had necessitated removal of at least 10 L of ascites in the 2 months preceding randomization for relief of symptoms.

The study was approved by the institutional Ethics Committee and written informed consent was obtained for all patients.

Exclusionary criteria were: inability to obtain informed consent, possible noncirrhotic ascites, congestive heart failure (defined by clinical exam and echocardiogram), acute renal failure, hepatocellular carcinoma [based on the Barcelona Clinic liver Cancer (BCLC) criteria],[13] complete portal vein thrombosis, active sepsis or other incurable cancers.

Each patient was assessed daily from admission until discharge with a complete objective examination, assessment of ascites grade [evaluated by International Ascites Club criteria[1] defining three grades: *grade* I *ascites,* fluid detected only by ultrasound; *grade* II, moderate ascites with symmetrical distension of the abdomen; *grade* III, large or tense ascites with marked abdominal distension], assessment of Child-Pugh score, measurement of blood pressure, heart rate, diuresis and body weight, clinical assessment of pleural effusion.

Blood samples were obtained every 3 days to determine serum electrolytes (sodium, potassium, chlorine), albumin, uric acid, urea, creatinine, prothrombin activity, activated partial thromboplastin time, fibrinogen, full blood counts, glucose and ammonia. Urine samples were collected to determine sodium and potassium excretion at admission and at discharge. All patients underwent a chest X-ray at admission and at discharge, a twelve derivation electrocardiogram at admission, while an abdominal echo-tomography was performed both at admission and at discharge to quantify ascites.

Patients were randomly assigned by the use of sequentially numbered boxes (prepared before starting the study by a computerized, non-alternating sequence) to the following groups:

(i) Group A: treatment with intravenous infusion of furosemide (doses 250–1000 mg/bid) plus small volumes of HSS (150 mL 1.4–4.6% NaCl), from the first day after admission until 3 days before discharge, with water restriction and a normal sodium diet.

(ii) Group B: repeated paracentesis (4 to 6 L daily) from the first day after admission until 3 days before discharge with albumin reinfusion at a rate of 5 to 8 g/L of removed ascites. The last paracentesis (at 3 days from admission) was a total paracentesis (8.7 ± 2.5 L) plus i.v. albumin infusion (8 g per litre of ascitic fluid removed) following a method previously described.[1] After last mobilization of ascites, patients were assigned to receive diuretic therapy with oral furosemide (increasing doses up to a maximum of 160 mg/day) and oral spironolactone (400 mg/day) was given. Water restriction and a normal sodium diet were given throughout the in-hospital stay.

Dosing of furosemide in Group A patients was governed by clinical parameters such as blood pressure and severity of ascites, while the concentration of hypertonic saline solution was calculated as a serum sodium value according to the following criteria:

(i) For serum sodium ≤125 mEq/L hypertonic saline solution at 4.6%. (787.2 mEq/L NaCl).

(ii) For serum sodium between 126 and 135 mEq/L hypertonic saline solution at 3.5% (599 mEq/L NaCl).

(iii) For serum sodium ≥136 mEq/L hypertonic saline solution between 1.4% and 2.4% (239.6–410.74 mEq/L NaCl).

Daily dosage of furosemide was reassessed according to diuresis, blood pressure and potassium levels.

Efficacy endpoints were:

(i) reduction in body weight (Δ body weight) at discharge;

(ii) relief of overt ascites at discharge 3 days after the end of diuretic treatment period or after last paracentesis (ascites graded at admission and at discharge according to International Ascites Club criteria);

(iii) improvement in Child Pugh score at discharge;

(iv) improvement in any co-existing fluid overload (leg oedema; pleural effusion) at discharge; (pleural effusion was evaluated clinically and by chest X-ray at discharge).

In Group A, achievement of these endpoints at 3 days from discharge determined the end of intravenous therapy and switching to oral furosemide (range 200–500 mg/die) and spironolactone (400 mg/day), while Group B continued therapy until discharge.

Safety endpoints were:

(i) new onset hepatic encephalopathy (HE);[18]

(ii) new onset spontaneous bacterial peritonitis (SBP);

(iii) acute renal failure in patients without renal impairment at admission, diagnosed by a serum creatinine level increasing by more than 50% over the baseline value or to above 1.5 mg/dL;[19]

(iv) impairment of pre-existing renal failure in patients with pre-existing renal impairment, diagnosed by serum creatinine increasing by more than 50% above baseline;[19]

(v) incidence of hepatorenal syndrome (HRS);[19]

(vi) incidence of gastrointestinal (GI) bleedings. Gastrointestinal bleeding refers to any bleeding that starts in the gastrointestinal tract, i.e. from the mouth to the large bowel:

(1) Upper GI bleeding: between the mouth and outflow tract of the stomach; (2) Lower GI bleeding: from the outflow tract of the stomach to the anus (small and large bowel included).

Statistical analysis

Results are presented as means ± s.d. Analyses of the data were performed using the unpaired Student's *t* test and the nonparametric test of Mann–Whitney. The chi-square test was used for comparing distributions and frequency of complications. All reported *P* values less than 0.05 were considered statistically significant.

To calculate the number of patients to be enrolled, we defined as meaningful a significant difference in detectable ascites frequency at discharge between the two groups, with a beta error of 20% and a power of 0.80. To the estimated sample size of 80 patients (60 in Group A and 20 in Group B), we added four more patients to compensate for possible drop outs; the final sample, therefore, comprised 84 patients.

RESULTS

We recruited 108 subjects with refractory ascites (73 with diuretic-resistant refractory ascites and 35 with diuretic-intractable refractory ascites). Twenty subjects were excluded on the basis of exclusion criteria and four patients refused to participate in the study. Eighty-four patients (59 men and 25 women) (58 with diuretic-resistant refractory ascites and 26 with diuretic-intractable refractory ascites) agreed to participate in the study and were randomized: 60 were assigned to Group A and 24 to Group B. The mean age was 64 ± 13.6 years in Group A and 64.8 ± 8.06 years in Group B (see Table 1).

In Group A, 42 patients (70%) had Hepatitis C (HCV) cirrhosis; four patients (6.6%) had Hepatitis B virus (HBV) cirrhosis; two (3.3%) had combined HCV/HBV cirrhosis; 11 (18.3%) had alcohol cirrhosis without viral infection and one patient had idiopathic cirrhosis. In Group B, 14 patients (58.3%) had HCV cirrhosis; three patients (12.5%) had HBV cirrhosis; five (20.8%) had combined HCV/HBV cirrhosis and two (8.3%) had alcohol cirrhosis.

In Group B, the mean number of paracentesis performed in the whole group was 2.7 ± 0.95 (range 1–4), the mean volume of ascites removed was 4.4 (±1.4) L.

At discharge, patients of Group A showed significantly higher diuresis and sodium plasma levels and significantly lower body weight and leg oedema and pleural effusion prevalence and median Child Pugh score; the median change in Child-Pugh score at discharge was significantly higher in Group A compared with Group B (−1.7 vs.−0.9; $P < 0.05$) (see Tables 2 and 3).

At discharge, 14 subjects (23.3%) in Group A had ascites (detected clinically or by ultrasound) vs. 11 (45.8%) in Group B.

No other significant difference was observed in terms of other laboratory and clinical variables between the two groups (ammonium, potassium plasma levels, new onset episodes of HE, incidence of gastrointestinal bleeding, acute renal failure or pre-existing renal failure progression, hepatorenal syndrome). There was no difference in hospital mortality between the two groups (see Table 3).

In Group A, no significant difference was observed between patients with the two subtypes of refractory ascites, diuretic-resistant and diuretic-intractable ascites.

DISCUSSION

Our pilot study showed how treatment with high-dose furosemide plus small-volume of HSS is safe and more effective compared with repeated paracentesis plus diuretic treatment in subjects with refractory ascites.

At the time of discharge, patients in Group A demonstrated significantly greater diuresis, higher plasma sodium levels, lower body weight, less leg oedema and smaller volume pleural effusion than Group B patients. This could be because of a more stable maintenance of volume reduction with high-dose diuretic treatment compared with repeated paracentesis.

Table 1. Demographic, clinical and laboratory characteristics of subjects with refractory ascites

	High-dose furosemide + HSS	Seriate paracentesis
Number of subjects	60	24
Gender (M/F)	39/21	14/10
Age (years) (mean ± s.d.)	64.8 ± 11.5	63. 9 ± 9.2
Aetiology of cirrhosis *n* (%)		
HBV	4 (6.6%)	3 (12.5%)
HCV	42 (70%)	14 (58.3%)
HCV/HBV	2 (3.3%)	5 (20.8%)
Alcohol-related	11 (18.3%)	2 (8.3)
Diuretic-resistant refractory ascites, *n* (%)	41 (68.3)	17 (70.8)
Diuretic-intractable refractory ascites, *n* (%)	18 (30)	8 (33.3)
Pre-treatment diuretics		
Furosemide, *n* (%)	60 (100)	24 (100)
Spironolactone, *n* (%)	60 (100)	24 (100)
Oesophageal varices (F1/F2/F3); *n* (%)	19 (31.6); 26 (43.3); 15 (25)	5 (20.8); 11 (45.8); 8 (33.3)
Bilirubin (mg/dL) (mean)	2.8 ± 0.9	3.0 ± 1
Albumin (g/L) (mean)	2.8 ± 4	2.6 ± 6
Prothrombin time (% of control)	41 ± 14	47 ± 17
INR	1.79 ± 1.3	1.80 ± 1.3
Sodium (mEq/L) (mean ± s.d.)	133 ± 1.4	134 ± 1.7
Potassium (mEq/L) (mean ± s.d.)	4.2 ± 0.8	4.3 ± 0.3
Diuresis (mL/24 h)	325 ± 147	412 ± 198
Hospital deaths (*n*/%)	2 (3.3)	1 (4.4)

Demographic and clinical data are expressed as number (percentage). Laboratory variables are expressed as mean ± s.d. HBV, hepatitis B virus; HCV, hepatitis C virus; Pre-treatment drugs, drugs used immediately prior to hospitalization or study enrolment.

Changes in body weight and urinary sodium determinations reflect response to treatment and represent a key outcome in patients with ascites. Our findings, through the evaluation of body weight, provide a direct outcome evaluation about the higher efficacy of high-dose furosemide + HSS treatment compared with repeated paracentesis.

Quintero *et al.*[2] analysed 72 cirrhotics with tense ascites randomly assigned to treatment with either paracentesis plus intravenous albumin infusion or diuretics and showed that paracentesis was not associated with significant changes in renal function. Gines *et al.*[26] showed how paracentesis was effective in eliminating the ascites and did not induce significant changes in renal and hepatic function, plasma volume, cardiac index, peripheral resistance and plasma renin activity (plasma norepinephrine, antidiuretic hormone concentration and urinary excretion of prostaglandin E2 and 6-keto-prostaglandin F1α). They also reported a significantly higher incidence of HE, renal impairment and electrolyte disturbances occurring in patients treated with diuretics. More recently, Salerno *et al.*[28] compared the effects of large-volume paracentesis and transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients with refractory ascites and showed that TIPS significantly improves ascites recurrence-free survival of cirrhotic patients with refractory ascites, although the cumulative probability of developing the first episode of HE was similar between the groups.

However, there are some disadvantages in repeated paracentesis. Ascitic fluid opsonic activity and ascitic fluid C3 concentrations are important protective factors against spontaneous bacterial peritonitis. Ljubicic *et al.*[27] compared the effect of diuretic administration alone vs. single large-volume therapeutic paracentesis followed by administration of diuretics on ascitic fluid opsonic activity on ascites and serum immunoglobulin and complement concentrations in patients with alcoholic cirrhosis and tense ascites. These authors showed that the ascitic fluid opsonic activity increased significantly in patients treated with diuretics alone, whereas in the group of patients treated with therapeutic

Table 2. Clinical and laboratory variables before (at admission) and after treatment with high-dose furosemide + HSS (Group A) or after seriated paracentesis (Group B)

	Furosemide plus HSS (*n*: 60)			Seriated paracentesis (*n*: 24)		
	Before	After	*P*	Before	After	*P*
Number of subjects	60	60		24	24	
Weight (kg)	78 ± 5.6	70 ± 7.4	<0.001	77 ± 3.8	73.8 ± 3.8	<0.001
Diuresis (mL/24 h)	550 ± 147	1805 ± 131	<0.05	580 ± 112	750 ± 124	0.07
Serum creatinin (mg/dL) (mean ±)	1.7 ± 0.5	1.45 ± 0.3	0.06	1.56 ± 0.6	1.76 ± 0.6	0.08
Uric acid (mg/dL) (mean ± s.d.)	4.4 ± 0.7	5.7 ± 0.4	0.05	4.2 ± 0.6	4.3 ± 0.2	0.79
Sodium (mEq/L) (mean ± s.d.)	133 ± 1.4	137 ± 3.8	0.88	134 ± 1.7	133 ± 4.6	0.73
Potassium (mEq/L) (mean ± s.d.)	4.2 ± 0.8	4.4 ± 0.6	<0.001	4.3 ± 0.3	4.2 ± 0.5	0.04
Urinary Na (mEq/24 h)	49.5 ± 9.4	158 ± 25	<0.05	47.8 ± 18	54.5 ± 12.4	0.70
Urinary K (mEq/24 h)	56.3 ± 7.6	83 ± 21	<0.05	54.3 ± 11.1	59 ± 29	0.63
Ascites *n* (%)	60 (100)	14 (23.,3)	<0.001	24 (100)	11 (45.8)	<0.001
Grade I	-	8 (13.3)	<0.001	-	-	
Grade II	14(23.3)	3 (5)	<0.001	5 (20.8)	9 (37.5)	0.032
Grade III	46(76.6)	3 (5)	<0.001	19 (79.1)	2 (8.3)	<0.001
Ammonium (mean ± s.d.) (μg/dL)	37 ± 7	38 ± 9	0.58	34 ± 7	34 ± 2	0.28
Leg oedema (*n*/%)	49 (81.6)	4 (6.6)	<0.001	18 (75)	16 (66.6)	0.04
Pleural effusion (*n*/%)	11(18.3)	2 (3.3)	<0.001	5 (20.8)	4 (16.6)	0.07
Child Pugh score (median)	9.2	7.6	0.037	9.8	8.9	0.045
HE (*n*/%)	9 (15)	8 (13.3%)	0.82	4 (16.6)	3 (12.5)	0.78
SBP (*n*/%)	-	-	-	-	2 (8.3)	0.05

Demographic and clinical data are expressed as number (percentage). Laboratory variables are expressed as mean ± s.d. HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; ascites grade was evaluated by Ascites International Club criteria.[5]

paracentesis followed by diuretics, the ascites opsonic activity remained stable. In our patients, we observed no case of SBP among those treated with high-dose furosemide + HSS and two cases of SBP among patients who underwent repeated paracentesis.

Cirrhotic patients with ascites refractory to diuretics also have blunted response to marked elevation of plasma atrial natriuretic factor levels alone or to moderate intravascular volume expansion by head-out water immersion. Wong *et al.*[29] reported that massive (as opposed to moderate) volume expansion or greatly elevated levels of plasma atrial natriuretic factor associated with moderate volume expansion can improve blunted atrial natriuretic factor responsiveness in cirrhotic patients with refractory ascites. Thus, volume expansion could represent a way to improve natriuretic response in patients with refractory ascites. A recent study by our group[30] showed that in patients with refractory congestive heart failure, treatment with HSS plus i.v. high-dose furosemide was associated with a significant reduction in BNP levels, thus suggesting possible use in refractory ascites. The formation of ascites in cirrhosis is the final consequence of a combination of abnormalities in the splanchnic and systemic circulation as well as renal function abnormalities that bring about the accumulation of fluid in the peritoneal cavity (forward theory).

The pathophysiological basis of higher efficacy of treatment with furosemide + HSS could be because of both volume expansion and improved reduction in sinusoidal portal pressure resulting in a fall in the plasma renin activity and serum aldosterone levels, a rise in renal blood flow and glomerular filtration rate associated with improved natriuresis. This effect occurs despite a possible exacerbation of the hyper-dynamic circulation, with a further fall in systemic vascular resistance and further increase in cardiac output. Nevertheless, it is possible that in our patients treated with furosemide + HSS, the HSS-related volume expansion served to compensate the 'underfilling' mechanisms that characterize ascitic cirrhosis. Small-volume HSS clearly induces an increase in the extracellular

Table 3. Comparison between the two groups treated with high-dose furosemide + HSS (Group A) or with seriate paracentesis. (Group B) regarding clinical and laboratory variables at discharge

	High-dose furosemide + HSS (*n*: 60)	Seriate paracentesis (*n*: 24)	*P*
Δ weight (kg)	−8.8 ± 4.8	−4.5 ± 3.8	<0.001
Diuresis (mL/24 h)	1805 ± 131	750 ± 124	<0.001
Serum creatinin (mg/dL) (mean ± s.d.)	1.45 ± 0.3	1.76 ± 0.6	0.08
Sodium (mEq/L) (mean ± s.d.)	137 ± 3.8	133 ± 4.6	0.04
Potassium (mEq/L) (mean ± s.d.)	4.4 ± 0.6	4.2 ± 0.5	0.78
Urinary Na (mEq/24 h)	158 ± 25	54.5 ± 12.4	<0.001
Urinary K (mEq/24 h)	83 ± 21	59 ± 29	<0.05
Ascites at discharge (*n*/%)	14 (23.3)	11 (45.8)	<0.001
Grade I*	8 (13.3)	-	<0.001
Grade II*	3 (5)	9 (37.5)	<0.001
Grade III*	3 (5)	2 (8.3)	0.029
Leg oedema (*n*/%)	4 (6.6)	16 (66.6)	<0.001
Pleural effusion (*n*/%)	2 (3.3)	4 (16.6)	<0.001
Child Pugh score (median)	7.6	8.9	0.04
Δ Child Pugh score (median)	−1.6	−0.9	<0.05
HE (*n*/%)	8 (13.3)	3 (12.5)	0.67
SBP (*n*/%)	–	2 (8.3)	
HRS (*n*/%)	4 (8)	2 (8.3)	0.54
GI bleedings (*n*/%)	3 (5.5)	1 (4.1)	0,07
pre-existing renal failure progression (*n*/%)	4 (8)	2 (8.3)	0.43
Acute renal failure (*n*/%)	2 (4)	1 (4.1%)	0.47
Hospitalization (days) (*n*/%)	9.4 ± 2.2	9.9 ± 2.0	0.68
Intrahospital deaths (*n*/%)	2 (3.3)	1 (4.4)	0.06

Demographic and clinical data are expressed as number (percentage). Laboratory variables are expressed as mean ± s.d.
Δ weight: body weight difference (body weight at admission – body weight after treatment with high-dose furosemide + HSS or seriate paracentesis); Δ Child Pugh score: Child pugh score change (Child Pugh score at admission – Child Pugh score at discharge).
* Ascites grade was evaluated by Ascites International Club criteria.[5]
HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; HRS, Hepathorenal Syndrome; GI bleedings, Gastrointestinal bleedings; Ascites at discharge, grade of ascites evaluated 3 days after end of diuretic treatment period or last paracentesis.

circulating concentration of NaCl with consequent increment in the osmotic pressure and in the plasmatic volume determining the fast redistribution of fluid in the vascular compartment with consequential increase in renal plasmatic flow.[12, 14, 17] Such fast expansion of the extracellular volume is also the cause of the reduction in the peritubular oncotic pressure that in combination with the increment of the hydrostatic pressure reduces the proximal reabsorption of the Na.[14, 15] HSS can determine an increase in the diuretic efficiency because HSS expands the arterial circulating volume and increases the distribution of the sodium after the proximal nephron until the thin portion of the ascending branch of the Henle loop, determining an increase in natriuresis.[14, 15] Another mechanism involved in the effectiveness of the HSS seems to be the restoration of normal production of renal E2 prostaglandin with restoration of the normal medullar tonicity usually altered by the chronic assumption of furosemide.[31, 32] Our findings emphasize the treatment with intravenous high-dose furosemide plus small volumes of HSS as effective and safe in patients with refractory ascites. An interesting finding is a slight, but not statistically significant, reduction in the creatinine levels (1.45 ± 0.3 mg/dL vs. 1.7 ± 0.5 mg/dL) in Group A patients, probably attributable to the benefits brought by this combination therapy to the hemodynamic and renal perfusion, but requiring ulterior evaluation in

prospective long-term studies. Nevertheless, although statistically insignificant, a potentially important finding of our study is that high-dose furosemide diuresis may not be as injurious to the kidney as high volume paracentesis and this finding contrasts with what has been a longstanding belief.

In contrast to previous studies,[20, 21, 22, 23–26] we did not observe a higher rate of hepatic encephalopathy (HE) in the group treated with high-dose furosemide. A combined derangement of cellular osmolarity coupled with cerebral hyperaemia can explain the development of brain oedema in HE.[33] It is possible that HSS infusion may influence cellular osmolarity to avoid increased incidence of HE in patients treated with high-dose furosemide, but future studies should evaluate this issue.

Our study showed that treatment with high-dose i.v furosemide + small-volume of hypertonic saline solutions is more effective compared with repeated paracentesis to achieve relief of ascites in patients with refractory ascites with a higher change of Child-Pugh Score and no significant differences between the two group in new onset HE frequency.

This is a pilot study conducted on consecutive patients with refractory ascites. Further studies are needed to confirm our findings and to evaluate hemodynamic and neurohormonal changes after treatment with high-dose furosemide + small-volume HSS and the possible relationship between these changes and therapeutic effectiveness of this type of treatment. Further studies are needed to test the effectiveness of this treatment protocol on a longer-term follow-up evaluation.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

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