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Clinical and Neurohumoral Response to Posture, Physical Exercise, and Ascites Treatment in Child-Pugh C Liver Cirrhosis: Randomized Prospective Trial

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Aim. To assess clinical and neurohumoral response to posture, physical exercise, and ascites treatment in patients with Child-Pugh C liver cirrhosis and tense ascites.

Method. Fifty patients with Child-Pugh C liver cirrhosis and tense ascites were randomly allocated into 5 groups. Thirty patients were treated with paracentesis of 6 L of acites paralleled by plasma volume expansion with 200 mL of 20% low sodium albumin (10 patients), 600 mL fresh frozen plasma (10 patients), or 900 mL solution of synthetic gelatine (10 patients), ie, doses with comparable oncotic power, and bed rest for 24 h before and after the procedure. They were compared with 10 patients treated with paracentesis of 6 L of ascites without plasma volume expansion and no bed rest, and 10 patients treated with 40 mg of furosemide IV daily and no bed rest. Mean arterial pressure, heart rate, body weight loss, urine flow rate, creatinine clearance, plasma renin activity, plasma aldosterone concentration, and plasma atrial natriuretic peptide (ANP) were measured before the procedure and 6 hours, 2, 3, and 6 days after the procedure.

Results. Diuretic treatment and paracentesis of 6 L of ascites without plasma volume expansion and no bed rest 24 h before and after the procedure were associated with significant hypotension ($p < 0.01$) during 6 days of the trial, tachycardia ($p < 0.01$) on day 1 and 2 ($p = 0.012$), lower total body weight loss ($p = 0.007$), increase in plasma renin activity 6 hours after the beginning of the study ($p = 0.025$) and on day 6 ($p = 0.024$), increase in plasma aldosterone concentration on day 6 ($p = 0.030$), no significant change in plasma ANP levels, and decrease in creatinine clearance on day 6 ($p = 0.046$). Albumin was superior to the other plasma expanders. Comparison between groups treated with plasma volume expansion did not show significant differences in measured parameters at any time during the study. The differences were found in the amount of needed volume of each substitute, daily sodium balance on day 1 of the trial, increase in plasma aldosterone concentration in bed rest-paracentesis-polygeline group on day 6, and the increase in plasma ANP on day 1 ($p = 0.077$), which was proportional to the amount of infused volume.

Conclusion. Therapeutic paracentesis of 6 L of ascites, bed rest 24 h before and after the procedure, and intravenous substitution of volume with albumin, fresh frozen plasma, and solution of synthetic gelatine were safe, rapid, and effective treatments, provided that intravascular volume was substituted simultaneously.

Key words: *ascites; bed rest; diuretics; liver cirrhosis; paracentesis; plasma volume*

Ascites is the most common complication of the advanced liver disease. In 80-85% of cases, it is related to alcohol-induced liver disease, mostly Laennec's cirrhosis (1,2). Ascites formation is the result of hemodynamic and neurohumoral changes in splanchnic and systemic vasodilatation in the natural course of liver cirrhosis (3). For a practicing physician, the question is when, how, and how fast ascites should be removed without deterioration of hepatic and/or kidney function (4). Therapeutic algorithms include low sodium diet, diuretics, paracentesis, transjugular intrahepatic portasystemic shunt, surgery, and extra corporal elimination (5,6).

The most controversial issue on therapeutic paracentesis is whether or not this procedure should be performed in association with plasma volume expansion to preent the effects of paracentesis on systemic hemodynamics. In this respect, opinions and approach of European (2,4-6,) and American (1) authors differ. The controversy is also reflected in different treatment algorithms that can be applied, which are 1) repeated taps of ascitic fluid 4-6 liters/day, with volume expansion (7); 2) total removal of all ascitic fluid, with volume expansion alone (8-10); 3) total removal of all ascitic fluid, with administration of diuretics after paracentesis to avoid reformation of ascites (11); 4) plasma volume expander, either albumin or colloids (12); and 5) none, due to contraindications for the procedure (2). Several randomized controlled studies of paracentesis showed an increase in effective arterial blood volume, cardiac output, and concentration of the plasma atrial natriuretic peptide (ANP), and decrease in plasma renin activity, plasma

aldosterone concentration, and plasma norepinephrine (8-10). However, this early phase was rapidly followed by a postparacentesis circulatory dysfunction syndrome, characterized by an irreversible reduction in effective arterial blood volume (5), with negative impact on the evolution of the disease (13). Critics of postparacentesis volume expansion (1) pointed out that patients treated with paracentesis and without volume expansion in the study by Gines et al (7) had statistically significant but clinically insignificant increase in plasma renin activity and creatinine clearance. There was no difference between the two groups in complication occurrence and mortality. However, another study showed that patients who develop postparacentesis circulatory dysfunction syndrome require higher doses of diuretics to prevent ascites formation, have a greater risk of ascites re-accumulation, and a shorter survival (14). The next important issue is necessity for bed rest in the ascites treatment protocol. Bernardi et al (15,16) showed that an increased total plasma volume depended upon the position of the body, physical activity, plasma aldosterone concentration, and was related to decreased natriuresis in up right posture in preascitic liver cirrhosis. Some authors think (2) that paracentesis is contraindicated in Child-Pugh C liver cirrhosis (17,18), whereas most of the patients with diuretic-resistant ascites and diuretic-intractable ascites (5) are from that class. The aim of our study was to compare the efficacy of proposed therapeutic protocols (7-10,19,20) in the management of cirrhotic patients with ascites by measuring their clinical and neurohumoral response.

Table 1. Child-Pugh classification* for the survival prognosis in liver cirrhosis

Parameter	Child-Pugh score A	B	C
Ascites	none	slight-moderate	tense
Hepatic encephalopathy (grade)	none	I-II	III-IV
Serum bilirubin (μmol/L)	<51	51-102	>102
Serum albumin (g/L)	>34	25-34	<25
Prothrombin time (%)	>60	46-60	<46
Grading	1	2	3
Score	6	7-9	10-15
Prognosis	good	variable	poor
Perioperative mortality (%)	5-6	28	55-60

*Child-Pugh score is a clinical instrument of survival prognosis for cirrhotic patients (17,18). The total score classifies patients into grade A, B, or C (ordinal scale) according to the points on continuous 5-15-point scale, which depends on ascites, encephalopathy, jaundice, serum albumin, and prothrombin time prolongation. The score assesses perioperative prognosis as good, variable, and poor; and perioperative mortality as percentage for each class.

Table 2. Inclusion and exclusion criteria for the enrollment of the patients in the study, with reasons for incomplete follow-up

Inclusion criteria:
- alcohol-induced Child-Pugh C liver cirrhosis with tense ascites
- clinical features of liver cirrhosis: jaundice, ascites, peripheral edema, hepatic encephalopathy, caput meduse, splenomegaly, spider angiomas, gynecomastia, testicular atrophy/virilization, menstrual irregularities, muscle wasting, palmar erythema
- ultrasonography features of liver cirrhosis: firm nodular liver, ascites, splenomegaly
- endoscopic findings of portal hypertension without recent bleeding
- laboratory markers of liver cirrhosis: hypoalbuminemia, hypofibrionogenemia, prolonged prothrombin time, pancitopenia
- sinus rhythm of the heart

Exclusion criteria:
- hepatic encephalopathy grade III and IV
- hepatocelular or metastatic liver carcinoma
- gastrointestinal bleeding within 4 weeks
- systemic infection (sepsis or peritonitis)
- serum creatinine ≥180 μmol/L
- platelet count $\leq 20 \times 10^9$/L
- serum sodium ≤125 μμολ/Λ
- chronic obstructive pulmonary disease
- heart failure

Reasons for exclusion after randomization:
- spontaneous bacterial peritonitis (pH<7.15 and/or L ≥250 in ascitic fluid)
- positive bacterial cultures of ascitic fluid

Subjects and Methods

Setting

The study was conducted at the Department of Medicine, Sisters of Mercy University Hospital, Zagreb, Croatia, from March 1998 to April 1999. The research was performed according to Good Clinical Practice and Helsinki Declaration principles (21), and approved by the Hospital's Ethical Committee and Drug Committee. All patients gave their written informed consent to participate in the study after a detailed explanation of the characteristics and purpose of the study.

Patients

Between March 1998 and April 1999, 83 cirrhotic patients were admitted to the Emergency Department of the Sisters of Mercy University Hospital for the treatment of an episode of tense ascites. The severity of cirrhosis was assessed by the Child-Pugh classification (17,18). Two investigators identified patients eligible for the study according to the following criteria: 1) alcohol-induced Child-Pugh liver cirrhosis with tense ascites (Table 1), 2) clinical features of liver cirrhosis, 3) ultrasonographic features of liver cirrhosis, 4) endoscopic signs of portal hypertension without recent bleeding, 5) laboratory markers of liver cirrhosis, and 6) sinus rhythm of the heart (Table 2). Out of 83 eligible patients, 31 were excluded due to the following reasons: coexisting hepatocellular carcinoma (n=8) or metastatic carcinoma (n=4), atrial fibrillation (n=4), hepatic encephalopathy grade III and IV (22) (n=1), gastrointestinal bleeding within 4 weeks (n=3), serum creatinine ≥180 μmol/L (n=1), platelet count $\leq 20 \times 10^9$/L (n=2), serum sodium ≤125 mmol/L (n=3), heart failure (n=2), and three patients who refused to participate in the study (Fig. 1).

Fifty-two patients admitted to the hospital were included in the study. They were kept on a diet containing 40 mEq/day sodium; liquid ingestion was restricted to 1L/day in patients with peripheral edema +2 and +3 (23) or serum sodium <130 mmol/L and diuretic treatment, cigarettes, alcohol, coffee, and tee were withdrawn. The use of diazepam, antibiotics, ranitidine, lactulose, and antacids was allowed where indicated. After diuretic discontinuation for 2-7 days (5 days on average), patients were randomly allocated by use of random number table into 5 groups of 10 to 11 patients (Fig.1).

Study Design

Patients in groups bed rest+paracentesis+albumin, bed rest+paracentesis+plasma, and bed rest+paracentesis+polygeline had 24-h bed rest on days 0 and 1. Patients in groups no bed rest+paracentesis and no bed rest+furosemide had no bed rest except for 2 h (6-8 a.m. on days 1, 2, 3, and 6, and 1-3 p.m. on day 1 before taking blood samples for plasma renin activity, plasma aldosterone concentration, and plasma atrial natriuretic peptide. Body height, weight, blood pressure, and heart rate were measured at 8 a.m. of the day 0 after overnight fasting from solid food, and blood samples were obtained from medial cubital vein to measure hemoglobin, prothrombin time, aspartat transaminase, alanin transaminase, serum bilirubin, albumin, urea, creatinine, and electrolytes. Urine was collected for 24 h to assess endogenous creatinine clearance as a measure of glomerular filtration rate; blood sample for serum creatinine was obtained at the end of collection time.

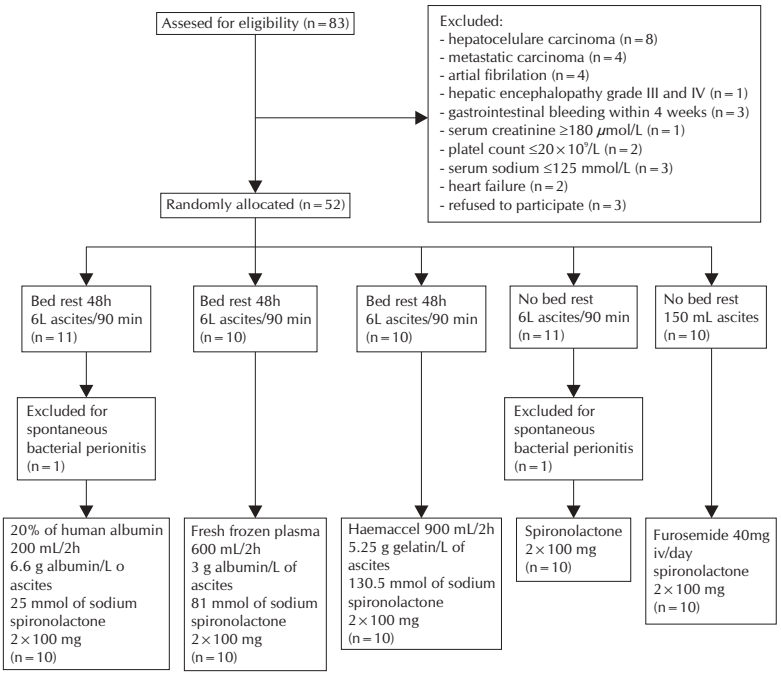

Figure 1. Flow of the patients through the study.

At 7 a.m. in the morning of day 1, after overnight fasting from solid food, an indwelling venous catheter was inserted in antecubital vein on each arm; one was used for blood sampling, and the other for drug and infusion administration by an infusion pump. Blood samples for plasma renin activity, plasma aldosterone concentration, and atrial natriuretic peptide were taken at 8 a.m. same day. Paracentesis was performed at 9 a.m. under strict sterile conditions with a Braun needle 176 1 3/4" 1.5×45 mm (B Braun Melsungen AG, Melsungen, Switzerland), and a sharp metal needle within cannula was inserted in the left lower abdominal quadrant. Once the needle entered the peritoneal cavity, the inner part was removed and ascitic fluid was drained by gravity into a sterile container on the floor. The process lasted for 2 h, or until the volume of collected ascitic fluid reached 6 liters, in all patient groups except in no bed rest + furosemide group, in whom 150 mL of ascitic fluid were drained. Ascitic fluid samples of all patients were analyzed immediately for leukocyte count, cytology, protein concentration, pH, and cultures. After the analysis, one patient from bed rest + paracentesis + albumin group and one from no bed rest + paracentesis group were excluded because of spontaneous bacterial peritonitis (Fig. 1). After the procedure, patients rested for 2 h in a reclined position on the right side to prevent leakage of ascites fluid. At the end of the ascites evacuation in patients from bed rest + paracentesis + albumin, bed rest + paracentesis + plasma, and bed rest + paracentesis + polygeline groups, infusion was started for the next 2 h, as follows: bed rest + paracentesis + albumin group received 200 mL of 20% low sodium albumin (Human-Albumin 20% Behring, Centeon Pharma GmbH, Marburg, Germany), with 6.6 g of albumin/L of ascites removed, and 25 mmol of sodium; bed rest + paracentesis + plasma group received 600 mL of fresh frozen plasma (Fresh Frozen Plasma, Croatian Institute of Transfusion Medicine; Zagreb, Croatia), with 3 g of albumin/L of ascites removed, and 81 mmol sodium; bed rest + paracentesis + polygeline group received 900 mL of polygeline (Haemaccel, Hoechst Marion Roussel, Horsholm, Denmark), with 5.25 g of polygeline/L of ascites removed, and 130.5 mmol of sodium (Fig. 1). One of the investigators always remained at the patient's bedside during the procedure. Patients in bed rest + paracentesis + albumin, bed rest + paracentesis + plasma, and bed rest + paracentesis + polygeline groups had bed rest for the next 24 h. Patients in the no bed rest + paracentesis group did not receive infusion and had no bed rest except for 2 h to prevent ascites leakage. Patients in no bed rest + furosemide group received 40 mg of furosemide (Fursemid ampule, Belupo, Koprivnica, Croatia) intravenously every morning at 9 a.m. All patients were treated with spironolactone (Aldactone capsule, Boehringer Mannheim, Wien, Austria) 2x100 mg on day 1 at 3 p.m. and 9 p.m. and on days 2-6 at 9 a.m. and 5 p.m. Measurements of blood pressure, heart rate, body weight, and urine volume were done every morning at 8 a.m. on days 2-6, and blood pressure and heart rate were measured on day 1 two, four, and six hours after the beginning of paracentesis. On day 1, 2, 3, and 6, urine was collected for 24 h to measure creatinine clearance. The accuracy of 24 h urine collection was checked by the determination of daily creatinine excretion. Blood samples for plasma renin activity, plasma aldosterone concentration, and atrial natriuretic peptide were obtained at 3 p.m. on day 1, and at 8 a.m. on days 2, 3, and 6 after supine position for at least 2 h and overnight fasting from solid food.

Assays

Blood pressure was measured with mercurial sphygomanometer (Riester, Jungingen, Germany). Mean arterial pressure, expressed in millimeters of mercury (mm Hg), was calculated as diastolic pressure (DP) plus one-third systolic pressure (SP) according to the following formula (24):

$$Mean\ arterial\ pressure = \frac{SP + 2DP}{3}\ (mm\,Hg)$$

Heart rate was expressed in beats per minute, body height (BH) in centimeters, body weight (BW) in kilograms (kg); ideal body weight was calculated by Lorenzo's formula (25), as follows:

$$Ideal\ body\ weight = (BH - 100) - \frac{BH - 150}{4}\ (kg)$$

Overweight was calculated as body weight (BW) and ideal body weight (IBW) difference, as follows:

Body overweight = BW – IBW (kg)

Urine volume was measured in milliliters. Creatinine clearance was calculated according to the following formula (26):

$$Creatinine\ clearance = \frac{U_{CR}\,x\,V_U}{S_{CR}}\ (mL/min),$$

where U_{CR} = creatinine concentration in 24-h urine (μmol/L), S_{CR} = serum creatinine (μmol/L), and V_U = urine output/24 h (mL/min) (26).

Blood samples in standard EDTA-K_3 containing tubes were used for hematological assays on Coulter-Counter S plus junior (Coulter Electronics Ltd., Luton, UK), prothrombin time was assessed by Quick method from blood samples in 3.8% sodium citrate tubes, 1:10 ratio, plasma was immediately separated by centrifugation (3000 G for 10 min) and analyzed automatically with Behring Coagulation Timer (Dade Behring, Marburg, Germany). Aspartat transaminase, alanin transaminase, serum bilirubin, albumin, urea, creatinine in serum and urine, and electrolytes were determined with commercially available kits on Olympus AU 600 and Olympus Fractoscan junior (Olympus Diagnostica GmbH, Hamburg, Germany).

For leukocyte count (Coulter-Counter S plus junior, Coulter Electronics Limited, Luton, UK) and standard biochemical tests (Olympus AU, Olympus Diagnostica GmbH), 150 mL of ascitic fluid was used. Ascites samples for cytological analysis were prepared from the sediment obtained by cytospin technology (1200 G for 2 min) on Shandon cyto 2 (Thermo Shandon, Pittsburgh, PA, USA). Sediment was immediately spread on a clean glass slide, air-dried for 20 min, and stained with Pappenheim method (May-Grünwald-Giemsa stain). All the slides were evaluated by the same cytologist using light microscopy. The cytological preparations of ascites were reviewed and classified as positive or negative according to the presence of tumor cells. Ascites fluid was cultured by the method of bed-side inoculation of blood culture bottles (FAN Aerobic and Anaerobic Culture Bottles, Organon Teknika Corp., Durham, Netherlands) with ascites. Microbiological analysis was preformed with microbial detection system (Organon Bact-Alert, Organon Teknika Corp.).

Blood samples for plasma renin activity, plasma aldosterone concentration, and atrial natriuretic peptide were collected in prechilled tubes (4 °C) containing EDTA–K_3 + aprotinin (Shionogi&Co, Ltd, Osaka, Japan) and centrifuged in a refrigerated centrifuge for 5 min at 8 °C (5000 G). Plasma was immediately divided into three tubes and frozen at -30 °C until the assay. Plasma renin activity was measured by angiotensin I radio immunoassay kit Ren-CT2 (CIS Bio International, Gif-sur-Yvette, France), and plasma aldosterone concentration was measured by solid-phase radioimmunoassay using reagent Aldo-Riact (CIS Bio International). Atrial natriuretic peptide (ANP) was measured by solid-phase "sandwich" immunoradiometric assay using Shionoria ANP kit (Shionogi&Co). Two monoclonal antibodies were prepared against sterically remote sites. The first was coated on the beads solid phase, whereas the second was radio labeled with iodine 125 and used as a tracer. Atrial natriuretic peptide molecules present in the standards or tested samples were "sandwiched" between the two antibodies. Excess unbound tracer was easily removed during the washing step, and the beads solid phase retained only the absorbed antibody/antigen/tracer antibody combination. The amount of radioactivity bound to the solid phase was proportional to the amount of atrial natriuretic peptide present at the beginning of the assay.

Statistical Analysis

Descriptive statistical methods were used for data analysis, and results were expressed as mean with standard deviation (mean ± SD) and median with range. We tested the differences between the groups using ANOVA, and homogeneity of variance using Leven test. For variables where variances were not homogenous, differences between the groups were tested with Kruskal-Wallis test. Qualitative variables were presented as frequency tables, and differences were tested with chi-square test. Level of statistical significance was set at $p < 0.05$. Repeated measurements were tested with ANOVA for repeated measurements and post-hoc multiple comparisons were done with Tukey HSD test. SAS System for Windows Release 6.12 (SAS Institute Inc., Cary, NC, USA). statistical software package was used for all data analyses.

Results

Out of 52 patients randomly allocated in 5 groups, 2 had to be excluded before receiving the therapy because of spontaneous bacterial peritonitis diagnosed at paracentesis (Fig. 1). Fifty patients, 37 men and 13 women, with mean age 54.30±8.47 years, remained in the study. The etiology of cirrhosis was alcohol-induced in all patients; 17 of them had concomitant hepatitis B and/or C. All patients had advanced liver disease and belonged to Child-Pugh C class (mean±SD points, 11.34±1.73). The severity of cirrhosis was indicated by the duration of the disease (4.0±3.8 years), high frequency of previous episodes of ascites, overweight (18.6±10.8 kg), hepatic encephalopathy (82%), large peripheral edema (84%), and tense ascites resistant to diuretic therapy. None of the patients had undergone therapeutic paracentesis for at least 10 days before the study. There was no significant difference between groups with respect to the clinical data (Table 3) and standard liver and renal function tests (Table 4), except for the severity of peripheral edema. There was no significant difference among the groups in baseline values of plasma renin activity, plasma aldosterone concentration, and

Table 3. Baseline epidemiological and clinical data of five studied groups of patients

	Bed rest + paracentesis groups			No bed rest groups			
Patient characteristics	albumin (n = 10)	plasma (n = 10)	polygeline (n = 10)	paracentesis (n = 10)	furosemide (n = 10)	Total (n = 50)	p
Alcohol etiology of cirrhosis	10	10	10	10	10	50	
Hepatitis B and/or C present	4	3	4	3	3	17	
Sex (men/women)	8/2	6/4	7/3	7/3	9/1	37/13	0.609*
Peripheral edema (+1/+2/+3)†	5/1/4	0/5/5	0/1/9	2/4/4	1/4/5	8/15/27	0.017*
Hepatic encephalopathy grade (0/I/II)‡	2/4/4	5/3/2	0/9/1	1/7/2	1/5/4	9/28/13	0.057*
Child-Pugh C score (median, range)§	12 (10-14)	12.2 (10-13)	12.5 (12-13)	12 (10-14)	12 (10-13)	12 (10-14)	0.360‖
Age (median, range; years)	51 (40-72)	54 (46-66)	52 (37-73)	57 (37-67)	53 (42-65)	54 (37-73)	0.921‖
Duration of the disease (years) (mean ± SD)	4.3 ± 3.5	6.3 ± 6.0	2.6 ± 2.0	4.2 ± 3.7	2.6 ± 2.0	4.0 ± 3.8	
(median, range)	3 (1-12)	4 (1-20)	2 (1-6)	3 (1-11)	2 (1-7)		0.416¶
Body weight (kg, mean ± SD)	89.9 ± 13.1	82.5 ± 10.8	84.7 ± 16.4	76.7 ± 8.6	78.6 ± 13.5	82.5 ± 13.1	
(median, range)	87 (71-112)	86 (65-101)	81 (64-125)	74 (64-92)	76 (66-114)		0.173‖
Body overweight (kg, mean ± SD)**	23.0 ± 10.5	18.4 ± 8.1	22.2 ± 14.4	14.4 ± 7.8	14.7 ± 11.1	18.6 ± 10.8	
(median, range)	19.8 (11.8-43.3)	19.8 (4.5-28.5)	16.5 (10.3-57.0)	14.5 (2.5-27.2)	13.9 (2.5-43.0)		0.233‖
Mean arterial pressure (mm Hg, mean ± SD)††	99.2 ± 18.4	105.3 ± 7.0	105.2 ± 12.1	98.0 ± 10.1	94.2 ± 10.2	100.4 ± 12.5	
(median, range)	100 (70-123)	105 (97-117)	108 (83-123)	98 (83-120)	93 (82-110)		0.106¶
Heart rate (beats/min, mean ± SD)	86 ± 15	79 ± 8	88 ± 13	88 ± 13	93 ± 16	87 ± 13	
(median, range)	82 (61-108)	77 (66-94)	89 (72-110)	86 (66-112)	89 (64-120)		0.934‖

*Chi-square test.
†Peripheral edema present (+1/+2/+3) (23).
‡Grade of hepatic encephalopathy (0/I/II) (22).
§Child-Pugh score (17,18).
‖ANOVA test.
¶Kruskal-Wallis test.
**Body overweight (25).
††Mean arterial pressure (24).

Table 4. Baseline hematological, biochemical, and neurohumoral data of the patients at enrollment in the study

	Bed rest + paracentesis groups			No bed rest groups			
Parameter (mean ± SD)	albumin (n = 10)	plasma (n = 10)	polygeline (n = 10)	paracentesis (n = 10)	furosemide (n = 10)	Total (n = 50)	p
Hemoglobin (g/L)	98.4 ± 11.4	102.9 ± 20.8	114.3 ± 10.2	101.0 ± 15.4	105.3 ± 17.8	104.4 ± 16.0	0.212*
(median, range)	96 (81-117)	109 (51-122)	115 (100-135)	99 (82-129)	104 (83-134)		
Prothrombin time (%)	54.3 ± 14.7	55.0 ± 20.6	42.7 ± 6.7	49.2 ± 17.5	46.6 ± 17.0	49.6 ± 16.1	0.391*
(median, range)	52 (33-78)	47 (36-91)	42 (30-53)	50 (16-75)	40 (31-78)		
Aspartate transaminase (U/L at 30°C)	48.9 ± 31.4	76.9 ± 60.3	64.1 ± 49.4	71.3 ± 59.4	61.2 ± 50.4	64.5 ± 50.0	0.905†
(median, range)	39 (13-103)	73 (9-198)	39 (19-176)	48 (26-209)	46 (19-188)		
Alanine transaminase (U/L 30°C)	22.7 ± 13.9	44.6 ± 63.5	29.6 ± 23.8	68.4 ± 104.4	42.0 ± 61.7	41.5 ± 61.9	0.977†
(median, range)	21 (5-52)	25 (4-220)	23 (11-78)	21 (9-310)	18 (10-210)		
Serum bilirubin (μmol/L)	56.8 ± 55.7	57.2 ± 28.7	70.2 ± 44.7	74.9 ± 39.8	77.3 ± 70.2	67.3 ± 48.6	0.820*
(median, range)	36.0 (13.3-186.5)	54.6 (7.9-104.2)	47.2 (32.6-148.8)	71.2 (27.8-130.2)	65.0 (12.3-245.6)		
Serum albumin (g/L)	28.44 ± 4.0	30.3 ± 4.6	28.5 ± 3.5	30.9 ± 3.8	28.6 ± 2.9	29.3 ± 3.8	0.447*
(median, range)	28.5 (22.5-36.3)	30.3 (23.7-37.8)	28.1 (24.6-33.8)	31.7 (24.8-36.2)	27.9 (25.1-34.7)		
Serum urea (mmol/L)	4.5 ± 3.8	4.6 ± 2.6	4.6 ± 1.9	4.5 ± 3.2	3.7 ± 2.0	4.4 ± 2.7	0.936*
(median, range)	3.2 (1.4-14.0)	4.3 (1.9-9.3)	4.0 (2.2-8.2)	3.4 (1.3-11.5)	3.8 (1.6-7.9)		
Serum creatinine (μmol/L)	100 ± 39	82 ± 33	82 ± 39	75 ± 15	68 ± 20	82 ± 32	0.617†
(median, range)	85 (54-154)	77 (49-165)	74 (32-161)	77 (49-96)	65 (34-100)		
Serum sodium (mmol/L)	134 ± 4	135 ± 5	135 ± 3	132 ± 4	134 ± 4	134 ± 4	0.299*
(median, range)	134 (130-140)	136 (128-143)	136 (127-138)	134 (126-136)	134 (127-138)		
Creatinine clearance (mL/min)	73 ± 30	71 ± 25	81 ± 17	65 ± 24	74 ± 31	73 ± 25	
(median, range)	70 (27-133)	76 (18-114)	81 (46-104)	59 (28-99)	69 (15-126)		0.706*
Urine output (mL/day)	940 ± 640	679 ± 441	735 ± 202	740 ± 194	870 ± 264	792 ± 384	0.547*
(median, range)	750 (400-2,600)	500 (300-1,800)	750 (450-1,200)	725 (450-1,100)	825 (450-1,250)		
Plasma renin activity (ng/mL/h)	8.0 ± 6.2	5.5 ± 10.7	5.4 ± 10.5	14.0 ± 15.6	8.8 ± 11.8	8.3 ± 11.4	0.298†
(median, range)	7.4 (0.2-16.9)	1.2 (0.1-35.0)	2.0 (0.5-35.0)	4.9 (0.3-35.0)	3.3 (0.2-35.0)		
Plasma aldosterone (pmol/L)	733 ± 978	518 ± 625	1,269 ± 1,808	1,688 ± 1,884	906 ± 1,073	1,023 ± 1,373	0.540†
(median, range)	273 (61-3,011)	269 (61-1,929)	317 (61-4,626)	467 (61-4,626)	622 (61-3,217)		
Atrial natriuretic peptide (pg/mL)	32 ± 28	38 ± 67	47 ± 97	19 ± 19	23 ± 18	32 ± 54	0.814†
(median, range)	17 (5-87)	12 (5-224)	8 (5-318)	9 (6-66)	18 (5-58)		

*Anova.
†Kruskal–Wallis.

plasma atrial natriuretic peptide, although all patients had pronounced increase in plasma renin activity, with almost doubled increase of plasma renin activity and plasma aldosterone concentration. There was a pronounced decrease in plasma atrial natriuretic peptide for patients without bed rest for 24 h before the study (Table 4).

Clinical and Laboratory Parameters

A slight, but significant decrease in mean arterial pressure was observed 2 h ($p = 0.022$), 4 h ($p = 0.019$), and 6 h ($p < 0.01$) after the onset of treatment, on days 2 ($p = 0.001$), 3 ($p < 0.01$), and 6 ($p < 0.01$) for no bed rest + paracentesis and no bed rest + furosemide groups (Fig. 2). This reduction in mean arterial pressure was clinically asymptomatic. There was a significant difference among the groups 2 h ($p = 0.020$), 4 h ($p < 0.01$) and 6 h ($p < 0.01$) after the start of the treatment, as well as on day 2 h ($p = 0.012$) in heart rate. Patients in no bed rest + paracentesis and no bed rest + furosemide groups had significantly lower total body weight loss on day 6 ($p = 0.007$). There was no significant difference among groups in serum creatinine during the trial. Daily urine output increased in all groups during the trial, with a significant difference on day 2 ($p = 0.002$) and day 3 ($p = 0.042$). The lowest values of daily urine output were recorded in no bed rest + paracentesis group. A significant decrease in creatinine clearance on day 6 ($p = 0.046$) was recorded in both no bed rest groups (Fig. 3).

Neurohumoral Parameters

To investigate possible occurrence of hypovolemia, we measured plasma renin activity, plasma aldosterone concentration, and plasma atrial natriuretic peptide as sensitive indicators of effective blood volume (13). Patients in bed rest + paracentesis + volume expansion groups had significant decrease in plasma renin activity 6 h after the onset of treatment ($p = 0.025$). Bed-rest groups significantly differed from no bed rest groups, regardless of the treatment they received ($p < 0.01$). Plasma renin activity increased significantly on day 6 in no bed rest groups ($p = 0.024$) (Fig. 4), as well as plasma aldosterone concentration ($p = 0.030$), which also increased in patients in bed rest + paracentesis + polygeline group (Fig. 5). After 48 h, no polygeline molecule is detectable in circulating blood; by the end of day 4, an average of 74% of the polygeline is excrated via the kidneys. Although we recorded low values of atrial natriuretic peptide in plasma of groups with no bed rest at baseline, there was no significant difference among the groups ($p = 0.814$). Lower values of plasma atrial natriuretic peptide at baseline conditions in no bed rest groups remained low during the trial. After volume expansion, there was a pronounced increase in plasma atrial natriuretic peptide ($p = 0.077$), correlating directly with the amount of infused volume (Fig. 6). Plasma atrial natriuretic peptide returned to baseline on day 6 in all groups ($p = 0.185$).

Complications

All patients were relieved of discomfort related to the tense ascites after paracentesis and 50 who received the therapy tolerated treatment protocols well and without any complications. No local complications related to the procedure were observed. Diuretics were effective in mobilizing the ascitic fluid in all patients in no bed rest + furosemide group. There was a significant difference between groups either in the development or in worsening of hepatic encephalopathy on day 6 ($p = 0.007$), with patients in no bed rest + furosemide group faring the worst. There were no significant changes in serum urea and creatinine concentrations, although increase in both was

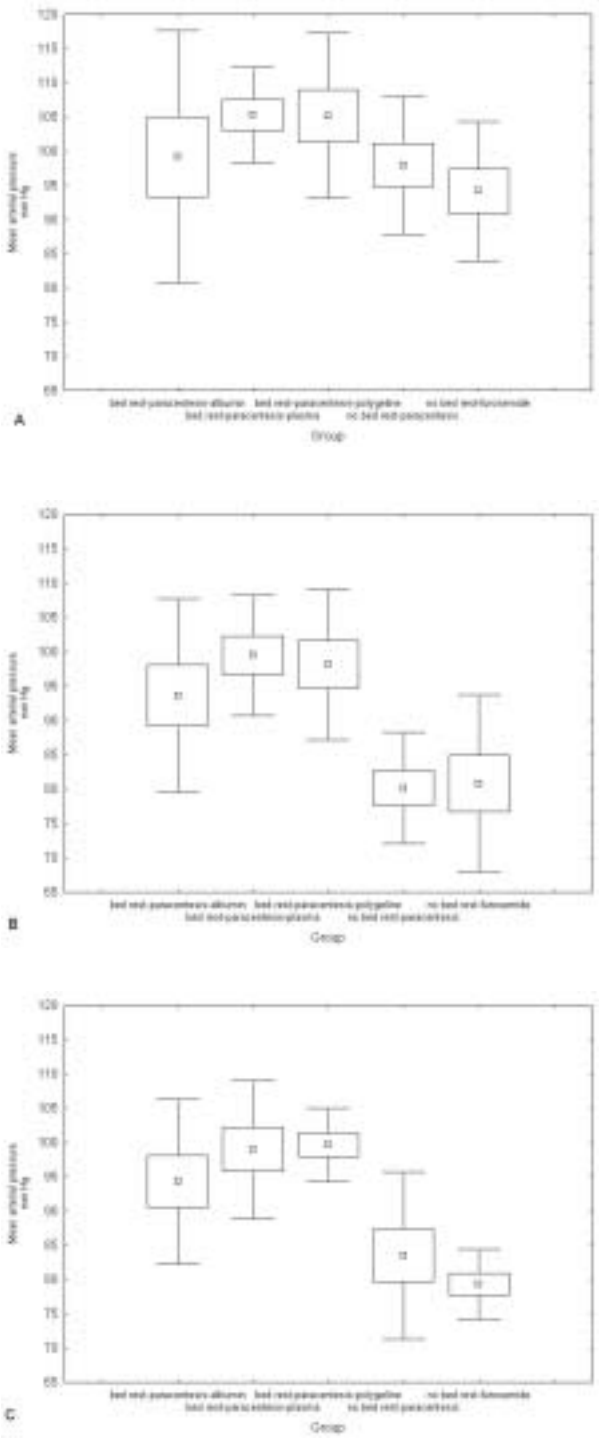

Figure 2. Mean arterial pressure during the trial. **A.** Baseline values. **B.** Six hours after the treatment. **C.** Day 6 of the treatment. Small squares – mean arterial pressure; large squares – standard error; Y error bars –standard deviations. Asterisks indicate significant differences ($p<0.05$) among groups.

recorded on day 6 in both no bed rest groups. Renal impairment was assessed on day 6 by measuring creatinine clearance ($p = 0.046$) in patients in both no bed rest groups (Fig. 3).

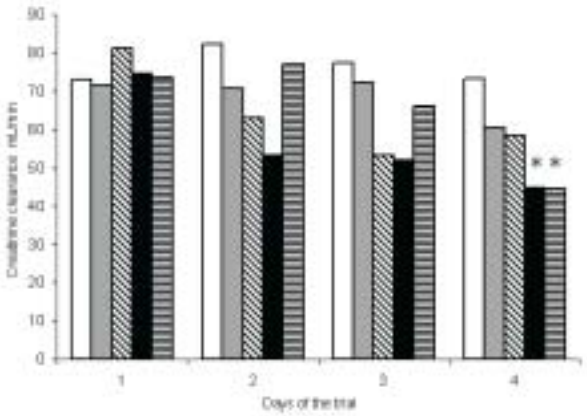

Figure 3. Creatininine clearance (mL/min) during the trial for five study groups. Open bars – bed rest + paracentesis + albumin group; dark gray bars – bed rest + paracentesis + plasma group; bars with slanted stripes – bed rest + paracentesis + polygeline group; closed bars – no bed rest + paracentesis group; bars with horizontal stripes – no bed rest + furosemide group. Asterisks indicate significant differences ($p<0.05$) among groups.

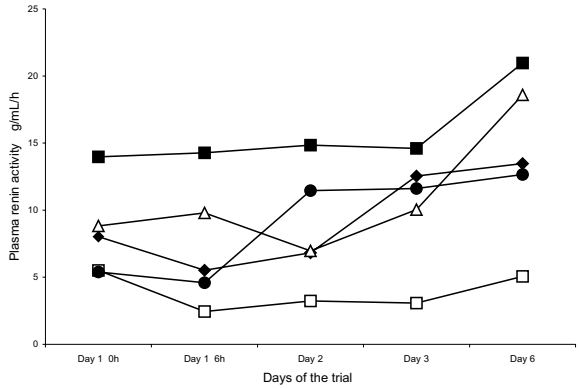

Figure 4. Plasma renin activity for five study groups during the trial. Closed rhombs – bed rest + paracentesis + albumin group; open squares – bed rest + paracentesis + plasma group; closed circles – bed rest + paracentesis + polygeline group; closed squares – no bed rest + paracentesis group; open triangles – no bed rest + furosemide group. Results are shown as mean values. Asterisks indicate significant differences ($p<0.05$) among groups.

Discussion

Therapeutic paracentesis of 6 L of ascites per day, associated with 24-h bed rest before and after the procedure was safe, rapid, and effective therapy for Child-Pugh C patients with liver cirrhosis and tense ascites, provided that intravascular volume was substituted simultaneously with albumin, fresh frozen plasma or solution of synthetic gelatine. It did not induce significant changes in clinical measurements and laboratory parameters of hepatic and renal function, plasma renin activity, and plasma aldosterone concentration. After removal of the ascites and plasma volume expansion, there was observable but not significant increase in the plasma atrial natriuretic peptide concentration. In contrast, paracentesis with-

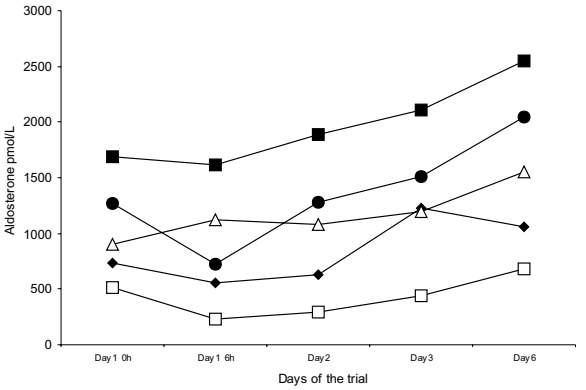

Figure 5. Plasma aldosterone concentration for five study groups during the trial. Closed rhombs – bed rest + paracentesis + albumin group; open squares – bed rest + paracentesis + plasma group; closed circles – bed rest + paracentesis + polygeline group; closed squares – no bed rest + paracentesis group; open triangles – no bed rest + furosemide group. Results are shown as mean values. Asterisks indicate significant differences ($p<0.05$) among groups.

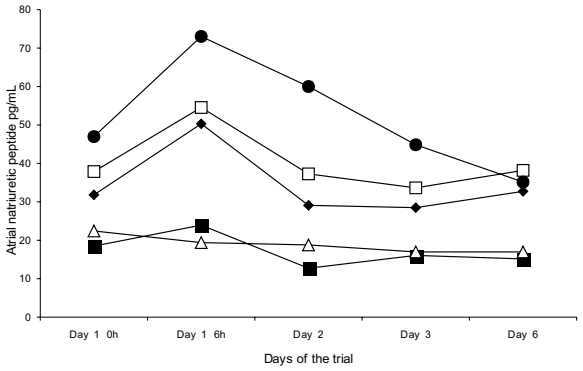

Figure 6. Plasma atrial natriuretic peptide (ANP) for five study groups during the trial. Closed rhombs – bed rest + paracentesis + albumin group; open squares – bed rest + paracentesis + plasma group; closed circles – bed rest + paracentesis + polygeline group; closed squares – no bed rest + paracentesis group; open triangles – no bed rest + furosemide group. Results are shown as mean values.

out 24-h bed rest before and after the procedure and plasma volume expansion was associated with significant increase in plasma renin activity, plasma aldosterone concentration, hypotension, tachycardia, lower total body weight loss, renal impairment, and no change in plasma atrial natriuretic peptide. Paracentesis combined with 24-h bed rest before and after the procedure and volume replacement was more effective than daily diuretic therapy, and was associated with a lower incidence of complications. The difference was mainly due to the higher incidence of hepatic encephalopathy in the former group. The hepatic encephalopathy caused by volume depletion during diuretic therapy occurred in patients with positive response to diuretics, particularly if peripheral edema was not present, and was rapidly reversible after discontinuation of therapy at day 6 of the trial. At present, the only effective method to prevent post-paracentesis circulatory dysfunction syndrome, predominantly caused by an accentuation of the arteriolar vasodilation already present in cirrhotic patients with ascites, is the administration of plasma expander (5,13,14). Panos et al (8) recorded hemodynamic changes induced by a single paracentesis in cirrhotic patients with tense ascites from whom 4-16 L of ascites were drained over 2 to 8 h. At 60 minutes, there was an increase in cardiac output compared with baseline, as well as a decrease in right atrium pressure, with no change in pulmonary capillary wedge pressure. Between 3 h and 12 h later, they had a significant decrease in cardiac output, pulmonary capillary wedge pressure, and right atrium pressure. At that point, plasma atrial natriuretic peptide concentration started to increase, whereas plasma renin activity and plasma aldosterone concentrations decreased. Twenty-four hours later, plasma atrial natriuretic peptide concentration was lower than the baseline, whereas plasma renin activity and plasma aldosterone concentrations showed increasing trend. The results indicated the development of relative hypovolemia and suggested that therapeutic plasma expansion was appropriate.

In Child-Pugh C cirrhotic patients with ascites, the physiological rhythm of plasma renin activity, plasma aldosterone concentration, and plasma atrial natriuretic peptide is preserved during supine and physical exercise (15,16,19,27). Extensive experimental data support the view that urinary sodium retention and plasma volume expansion precedes the formation of ascites. Sodium retention is required to maintain effective arterial blood volume as blood becomes sequestrated within the portal venous circulation. Intrahepatic sinusoidal hypertension is a significant source of preascitic sodium retaining signals to the renal tubule (28). Investigations by Bernardi et al (15,16) showed that an increased total plasma volume depends upon the position of the body, physical activity, and plasma aldosterone concentration. The increase in plasma aldosterone concentration and decrease of natriuresis in the upright posture is a likely compensatory mechanism for the increase in the total plasma and blood volume under conditions of an enlarged splanchnic basin in portal hypertension development. Moderate physical exercise does not affect glomerular filtration rate and renal excretory function in healthy subjects. Salo et al (27) showed that moderate cycloergometric exercise in sitting position in nonazotemic cirrhotic patient with ascites was associated with significant increase in arterial pressure, heart rate, plasma renin activity, plasma aldosterone concentration, and plasma norepinephrine. The plasma atrial natriuretic peptide concentration did not change. Moderate physical exercise had no detrimental effects on renal function in cirrhotic patient with ascites and no or mild activation of the renin-aldosterone and sympathetic nervous systems. However, it caused a pronounced impairment in the renal function of patients with ascites and pronounced stimulation of these vasoconstrictor systems.

An important observation in our study was an increase in plasma concentrations of atrial natriuretic

peptide after plasma volume expansion. Atrial natriuretic peptide is thought to be released from cardiac atria by multiple mechanisms. In vitro mechanical stretch of atrial tissue produces an increased release of atrial natriuretic peptide. In animal studies, atrial pressure (29) and/or stretch (30), frequency of atrial contractions (29), intravascular volume (31) and baroreceptor activity (32) were all shown to play a role, although atrial stretch was probably the most important. In human pathophysiological states, atrial pressure is undoubtedly the most important factor (29). Because atrial distension clearly mirrors the changes in intravascular volume, plasma concentrations of atrial natriuretic peptide are thought to serve as sensitive indicator of fullness of the circulation, increasing with intravascular volume expansion and decreasing with volume contraction. In patients with liver cirrhosis, plasma concentrations of atrial natriuretic peptide are attributable to several factors: high blood volume, effective hypovolemia, hyperdynamic circulation, intra-abdominal and intra-thoracic pressure, posture, sodium intake, and drug administration. In advanced stages of liver cirrhosis with ascites, plasma atrial natriuretic peptide concentrations were reported as increased, normal, or decreased. As the disease progresses and intrahepatic pressure increases, progressive urinary sodium retention causes plasma volume expansion, which causes increase in plasma atrial natriuretic peptide concentration. Epstein et al (33) showed that decreased tubular responsiveness to atrial natriuretic peptide may cause exaggerated increase in plasma concentrations of atrial natriuretic peptide secreted by cardiac atria.

In our study, there was no significant difference in baseline plasma atrial natriuretic peptide concentrations between groups. Increase in the plasma atrial natriuretic peptide, recorded in groups with plasma volume expansion on day 1, was proportional to the amount of volume replacement (Fig. 6). Cardiac release of atrial natriuretic peptide in response to volume expansion was not impaired in patients with Child-Pugh C liver cirrhosis and tense ascites. This was achieved by exaggerated release of atrial natriuretic peptide coupled with suppression of the renin-aldosterone axis, as a result of the supine induced expansion of central volume, and beneficial hemodynamic effect of paracentesis with simultaneous plasma volume expansion. The main mechanism stimulating the acute release of atrial natriuretic peptide was atrial stretching induced by volume replacement, and it was proportional to its amount.

In conclusion, our study showed that paracentesis of 6 L of ascites, with 24-h bed rest before and after the procedure and plasma volume expansion, was the best treatment algorithm for Child-Pugh C patients with liver cirrhosis and tense ascites. Albumin was superior to other plasma expanders in all aspects except cost. However, volume replacement with plasma derivatives is hazard for virus transmission (1). Comparisons between groups treated with plasma volume expansion did not show significant differences, except for the amount of needed volume of each substitute, daily sodium balance on day 1 of the trial, increase in plasma aldosterone concentration in bed rest + paracentesis + polygeline group on day 6, and increase in plasma atrial natriuretic peptide on day 1 proportional to the amount of infused volume. After mobilization of ascites by paracentesis, patients should receive diuretics immediately after the procedure to prevent early recurrence of ascites. The administration of 200 mg of spironolactone per day was a good empiric treatment for non-azothemic patients with cirrhosis, because it was effective in most cases and did not increase the incidence of postparacentesis circulatory dysfunction syndrome. A patient should be observed for at least 6 days after large volume paracentesis because of possible progressive deterioration of renal function (measured as creatinine clearance), worsening of electrolyte imbalance, and development or worsening of hepatic encephalopathy.

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