Randomized Trial Comparing Albumin, Dextran 70, and Polygeline in Cirrhotic Patients With Ascites Treated by Paracentesis

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Background & Aims: **Paracentesis associated with plasma expanders is widely used for the treatment of ascites in cirrhosis. This study investigated the clinical importance of paracentesis-induced circulatory dysfunction and compared the efficacy of albumin, dextran 70, and polygeline in preventing this complication.** ***Methods:*** **A total of 289 cirrhotic patients with ascites were randomized to treatment by total paracentesis plus intravenous albumin (97 patients), dextran 70 (93 patients), or polygeline (99 patients). Postparacentesis circulatory dysfunction was defined as an increase in plasma renin activity on the sixth day after paracentesis of more than 50% of the pretreatment value to a level >4 ng $\cdot$ mL^{-1} $\cdot$ h^{-1}.** ***Results:*** **Postparacentesis circulatory dysfunction occurred more frequently in patients treated with dextran 70 (34.4%; $P = 0.018$) or polygeline (37.8%; $P = 0.004$) than in those receiving albumin (18.5%). The plasma expander used and the volume of ascites removed were independent predictors of this complication. Postparacentesis circulatory dysfunction persisted during follow-up and was associated with a shorter time to first readmission (1.3 $\pm$ 0.5 vs. 3.5 $\pm$ 0.8 months, median $\pm$ SEM; $P = 0.03$) and shorter survival (9.3 $\pm$ 4.2 vs. 16.9 $\pm$ 4.3 months; $P = 0.01$). Creatinine and sodium levels in serum, and Child–Pugh score at inclusion, and postparacentesis circulatory dysfunction were independent predictors of survival.** ***Conclusions:*** **Postparacentesis circulatory dysfunction is not spontaneously reversible and is associated with a shorter time to first readmission and shorter survival. Albumin is the best plasma expander to prevent this complication.**

Paracentesis associated with plasma volume expansion is an effective and safe therapy of tense ascites in cirrhosis. Four randomized trials have shown that it is more effective than diuretics, is associated with lower rate of complications, reduces the time of hospitalization, and does not affect the long-term course of the disease.[1–4] Other investigations have subsequently confirmed these data.[5–9]

When paracentesis is performed without plasma volume expansion, a circulatory dysfunction that leads to a marked activation of the renin-angiotensin-aldosterone system and may be associated with an impairment in renal function frequently develops.[10–14] Because these changes are prevented by intravenous infusion of albumin,[10,11,15] paracentesis is generally performed in association with the administration of this plasma expander. However, the clinical relevance of postparacentesis circulatory dysfunction is not known.[16,17] The use of synthetic plasma expanders, such as dextran 70, dextran 40, or polygeline, after therapeutic paracentesis is another aspect that remains controversial. Some investigations suggest that albumin is more effective than the synthetic plasma expanders in preventing postparacentesis circulatory dysfunction, but a similar efficacy has been observed in other studies.[4,16,18,19]

In this article, we report the results of a multicenter trial of cirrhotic patients with tense ascites who were

Abbreviation used in this paper: PRA, plasma renin activity.

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randomly assigned to groups receiving albumin, dextran 70, or polygeline as plasma expanders after total paracentesis. The aims of the study were to compare the efficacy of these plasma expanders in preventing postparacentesis circulatory dysfunction and to investigate whether postparacentesis circulatory dysfunction has any impact on morbidity or mortality.

Patients and Methods

We studied 289 patients with cirrhosis who were admitted for tense ascites in 12 hospitals. The diagnosis of cirrhosis was based on histological analysis of the liver in 218 patients and on clinical and laboratory data and ultrasonography in 71. Patients with a serum bilirubin level of >10 mg/dL, prothrombin time of <40%, platelet count of <40,000/mm^3, serum creatinine concentration of >3 mg/dL, gastrointestinal hemorrhage within the preceding month, hepatocellular carcinoma, or respiratory, cardiac, or renal disease were excluded. Patients treated with propranolol for prophylaxis of variceal bleeding or rebleeding were also excluded. Patients with tense ascites hospitalized for hepatic encephalopathy or bacterial infection were considered candidates for the trial after they had recovered from these complications. The study was approved by the Investigation and Ethics Committee of each hospital, and all patients gave informed consent to participate.

Patients were studied after they received a low-sodium diet (50 mmol/day) without any diuretic therapy for 5 days. On the sixth day, samples were obtained to determine liver and renal test results and plasma renin activity (PRA). Samples for PRA were obtained and processed as described previously.[1] Patients at each hospital were then randomly assigned to one of three groups using sealed envelopes containing the treatment options prepared with a random number table. Group I consisted of 97 patients who were treated with total paracentesis (complete removal of ascites in a single tap) and intravenous albumin (8 g/L of ascitic fluid removed, with 50% of the dose within the first 2 hours and 50% 6–8 hours after paracentesis; Albumina Humana Grifols, 20% albumin solution; Instituto Grifols S.A., Barcelona, Spain). Group II consisted of 93 patients treated with total paracentesis and intravenous dextran 70 (8 g/L of ascitic fluid removed using the same schedule as for albumin; Macrodex 6% Glucosado containing 6 g of dextran 70 per 100 mL of glucose solution; Instituto de Biología y Sueroterapia Ibys, Madrid, Spain). Group III consisted of 99 patients treated with total paracentesis and intravenous polygeline (8 g/L of ascitic fluid removed using the same schedule as for albumin; Hemoce, 3.5% saline solution of polygeline; Behring-Hoechst Ibérica, Barcelona, Spain). The amount of colloid infused and rate of infusion were selected on the basis of previous studies.[1,5,6,19] Randomization was independent for each hospital, and patients with and without renal impairment (serum creatinine value of >1.5 mg/dL) were randomized separately.

Paracentesis was performed as described in detail elsewhere.[5] After treatment, patients did not receive diuretics for 6 days. Liver and renal tests and PRA measurements were repeated 2 and 6 days after treatment. Patients were discharged from hospital with diuretics. The dosage of these drugs was subsequently adjusted according to individual responses.

The follow-up period started at the end of the first hospitalization. Patients were examined in the outpatient clinic at least weekly during the first month, monthly for the next 2 months, and bimonthly thereafter. PRA was measured 1 and 6 months after discharge in 122 and 58 patients, respectively. Patients in whom tense ascites developed during follow-up were treated with total paracentesis and the same plasma expander assigned at inclusion.

Postparacentesis circulatory dysfunction was estimated through changes in the activity of the renin-angiotensin system and defined as an increase in PRA of more than 50% of the pretreatment value to a level of >4 ng · mL^{-1} · h^{-1} on the sixth day after paracentesis. This latter figure is the upper value of PRA found in 36 healthy subjects studied on a 50-mmol/day sodium diet. This definition, which was decided before the initiation of the study, takes into account both the changes in the activity of the system and the final activity after paracentesis and was arbitrarily chosen to detect a physiologically relevant activation of the renin-angiotensin system. Renal impairment and hyponatremia after treatment were defined using previously described criteria.[6]

Methods of Measurement

PRA was measured by radioimmunoassay.[6] Other measurements were made using standard laboratory techniques. The normal value (mean ± SD) for PRA in 36 healthy volunteers on a 50-mmol/day sodium diet for 7 days was 1.35 ± 0.94 ng · mL^{-1} · h^{-1} (range, 0.1–4.0 ng · mL^{-1} · h^{-1}).

Statistical Analysis

The main end point chosen to calculate the sample size was the development of postparacentesis circulatory dysfunction. It was calculated that 100 patients per group were needed to detect a difference of 20% in the proportion of patients developing circulatory dysfunction, at least between groups I and II (20% and 40%, respectively), with an α error of 5% and a β error of 10%. Categorical data were evaluated by χ^2 tests, and continuous data were compared by paired and unpaired Student's t tests. Multiple comparisons were performed with the analysis of variance and the Newman–Keuls test for continuous data and χ^2 tests for categorical data. Probability curves were constructed by the Kaplan–Meier method and compared with the Mantel–Cox test. Univariate analysis to identify variables predicting the development of postparacentesis circulatory dysfunction was performed using χ^2 tests for qualitative variables and Student's t test for quantitative variables. Univariate analysis to identify variables predicting survival was performed comparing survival probability curves.

Table 1. Clinical and Laboratory Data at Baseline in the Three Groups of Patients With Cirrhosis and Ascites

Characteristic	Group I (albumin; n = 97)	Group II (dextran 70; n = 93)	Group III (polygeline; n = 99)
Age (*yr*)	59 ± 10[a]	57 ± 10	57 ± 10
Sex (M/F)	67/30	63/30	71/28
No. with alcohol abuse	70	63	69
No. with previous episodes of			
Ascites	64	63	59
Encephalopathy	13	15	18
Gastrointestinal bleeding	20	19	13
Cause of admission			
Ascites alone	82	83	88
Ascites plus other causes[b]	15	10	11
No. with peripheral edema	63	56	62
No. with renal impairment[c]	19	15	17
Serum bilirubin (*mg/dL*)	2.8 ± 2.1	2.8 ± 2.0	2.7 ± 2.2
Prothrombin time (*%*)	58 ± 14	58 ± 16	61 ± 16
Serum albumin (*g/dL*)	2.7 ± 0.5	2.6 ± 0.5	2.6 ± 0.5
Serum creatinine (*mg/dL*)	0.9 ± 0.3	0.9 ± 0.3	1 ± 0.5
Serum sodium (*mEq/L*)	132 ± 6	133 ± 6	133 ± 6
Urinary sodium (*mEq/day*)	7 ± 6	6 ± 7	7 ± 7
Mean arterial pressure (*mm Hg*)	82 ± 11	84 ± 11	84 ± 13
Child–Pugh score[d]	10 ± 1.3	10 ± 1.4	10 ± 1.4
PRA ($ng \cdot mL^{-1} \cdot h^{-1}$)	9.2 ± 10.3	9.5 ± 11.7	8.6 ± 9.8

NOTE. There were no significant differences in baseline values among the groups.
[a]Values (±) are means ± SD.
[b]Hepatic encephalopathy, bacterial infections (mainly spontaneous bacterial peritonitis), and other causes.
[c]Renal impairment was defined as a serum creatinine level of >1.5 mg/dL.
[d]The Child–Pugh score (range, 5–15) was calculated on the basis of the presence and degree of hepatic encephalopathy, presence and degree of ascites, bilirubin and albumin concentration in serum, and prothrombin time.[21]

To identify independent predictors of development of postparacentesis circulatory dysfunction or survival, variables reaching statistical significance ($P < 0.05$) in the univariate analysis were introduced in a multivariate analysis using stepwise logistic regression or Cox regression procedure, respectively. All these calculations were made using the BMDP statistical package.[20] Results are presented as mean ± SD unless indicated. All reported P values are two tailed, with values of <0.05 considered significant.

Results

Characteristics at Inclusion and Results During First Hospitalization and Follow-up in the Three Therapeutic Groups

No significant differences in clinical and laboratory data were noted among the patients in the three groups at inclusion (Table 1).

Table 2 shows the results during the first hospitaliza-

Table 2. Number and Types of Complications During First Hospitalization in Patients in the Three Groups

	Group I (albumin; n = 97)	Group II (dextran 70; n = 93)	Group III (polygeline; n = 99)
Duration (*days*)	18 ± 28	15 ± 11	17 ± 43
No. of patients with complications	28	28	30
No. of complications	30	43	39
Hyponatremia	14	23	19
Renal impairment	7	8	10
Hepatic encephalopathy	3	5	5
Gastrointestinal bleeding	1	4	1
Bacterial infection	5	3	3
Other	0	0	1
No. of patients with postparacentesis circulatory dysfunction[a]	17/92[b]	31/90	37/98
No. of patients who died	2	4	6

[a]Figures represent the number of patients who developed postparacentesis circulatory dysfunction and the number of patients who had PRA measured at baseline and 6 days after the procedure.
[b]Comparison between groups I and II and I and III: $P = 0.018$ and $P = 0.004$, respectively.

Table 3. Arterial Pressure and Laboratory Parameters Before and 6 Days After Paracentesis in the Three Groups

Variable	Group I (albumin)		Group II (dextran 70)		Group III (polygeline)	
	Before	6 days after	Before	6 days after	Before	6 days after
Mean arterial pressure (*mm Hg*)	82 ± 11	79 ± 11[b]	84 ± 11	81 ± 11[b]	84 ± 13	80 ± 11[c]
Hematocrit (*%*)	32 ± 6	32 ± 7	33 ± 6	33 ± 6	33 ± 6	33 ± 6
Serum creatinine (*mg/dL*)	0.94 ± 0.3	0.97 ± 0.4	0.89 ± 0.3	0.95 ± 0.3[a]	0.98 ± 0.5	1.09 ± 0.8[b]
Serum sodium (*mEq/L*)	132 ± 6	132 ± 6	132 ± 6	131 ± 6[b]	133 ± 6	131 ± 6[b]
PRA ($ng \cdot mL^{-1} \cdot h^{-1}$)	8.8 ± 10.3	9.3 ± 10.9	9.2 ± 11.2	12.7 ± 13.4[c]	8.6 ± 9.8	11.6 ± 12.8[b]

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ vs. baseline values.

tion. The volume of ascites removed was 7.5 ± 2.5, 7.7 ± 2.9, and 8.2 ± 3.6 L in groups I, II, and III, respectively (P = NS). There were no significant differences between the groups in duration of hospital stay and incidence and type of complications, although the number of complications was slightly higher in the nonalbumin groups. The effect of paracentesis on PRA could be assessed in 280 patients. Postparacentesis circulatory dysfunction occurred with a significantly greater frequency in patients treated with dextran 70 (34.4%) and polygeline (37.8%) than in those treated with albumin (18.5%) (relative risk, 1.5 and 1.6; 95% confidence interval, 1.12–1.98 and 1.21–2.06, respectively). The effect of paracentesis on arterial pressure and laboratory parameters is shown in Table 3. Arterial pressure decreased to a similar degree in the three groups. No significant change in hematocrit was observed in any group. Creatinine level in serum and PRA increased and sodium level in serum decreased significantly only in groups II and III. The mortality rate during the first hospital stay was very low in the three groups (Table 2).

Of the 277 patients surviving to time of discharge, 27 were lost to follow-up after a period ranging from 1 to 30 months. Fourteen other patients underwent liver transplantation 1–15 months after discharge. These patients were considered censored at the time of surgery. The remaining 236 patients were followed up to the end of the study or death. During follow-up (mean follow-up, 302 ± 241, 293 ± 268, and 269 ± 262 days in albumin, dextran 70, and polygeline groups, respectively), no significant differences were found among the groups in the number of patients requiring readmission, causes of readmission, and deaths.

Clinical Course of Patients Who Did and Did Not Develop Postparacentesis Circulatory Dysfunction

Of the 280 patients with measurements of PRA before and 6 days after treatment, 85 developed postparacentesis circulatory dysfunction. PRA in these patients increased from 8.0 ± 7.4 to 18.6 ± 14.8 $ng \cdot mL^{-1} \cdot h^{-1}$ ($P < 0.0001$). The corresponding values in patients not developing postparacentesis circulatory dysfunction were 9.3 ± 11.5 and 8.0 ± 9.8 $ng \cdot mL^{-1} \cdot h^{-1}$ (P = NS). In patients developing circulatory dysfunction, a significant increase in PRA was also observed 2 days after treatment (15.7 ± 15.9 $ng \cdot mL^{-1} \cdot h^{-1}$; $P < 0.001$ vs. baseline). However, although the specificity of this measurement for the diagnosis of circulatory dysfunction after paracentesis was relatively high (86%), its sensitivity was poor (55%). Of the 85 patients who developed postparacentesis circulatory dysfunction, only 47 showed a marked increase (>50%) in PRA above 4 $ng \cdot mL^{-1} \cdot h^{-1}$ on the second day of treatment. No significant changes in PRA were observed in patients not developing postparacentesis circulatory dysfunction.

Figure 1 shows PRA during the first hospitalization and 1 and 6 months after discharge in all patients divided according to the development of postparacentesis circulatory dysfunction. In patients developing this condition, the initial increase in PRA persisted during the entire follow-up period. This persistent increase in PRA was probably not caused by the repeated treatment with paracentesis because PRA remained increased even in patients who did not require further paracentesis during follow-up. PRA values in patients with sequential measurements up to 1 month (n = 9) were 3.2 ± 2.4 at baseline, 6.9 ± 6.8 at 48 hours, 10.9 ± 7.1 at 6 days, and 17.4 ± 10.2 $ng \cdot mL^{-1} \cdot h^{-1}$ at 1 month ($P < 0.01$); in patients with sequential measurements up to 6 months (n = 5), they were 3.4 ± 2.8 at baseline, 9.5 ± 8.4 at 48 hours, 11.9 ± 8.1 at 6 days, 12.9 ± 6.2 at 1 month, and 10.2 ± 4.6 $ng \cdot mL^{-1} \cdot h^{-1}$ at 6 months ($P < 0.05$). In contrast, changes in PRA during follow-up were minimal in patients not developing circulatory dysfunction. No significant differences in the length of stay and incidence of complications during the first hospitalization were found between patients who did and did not develop postparacentesis circulatory dysfunction, except for a higher frequency of hyponatremia in patients from the

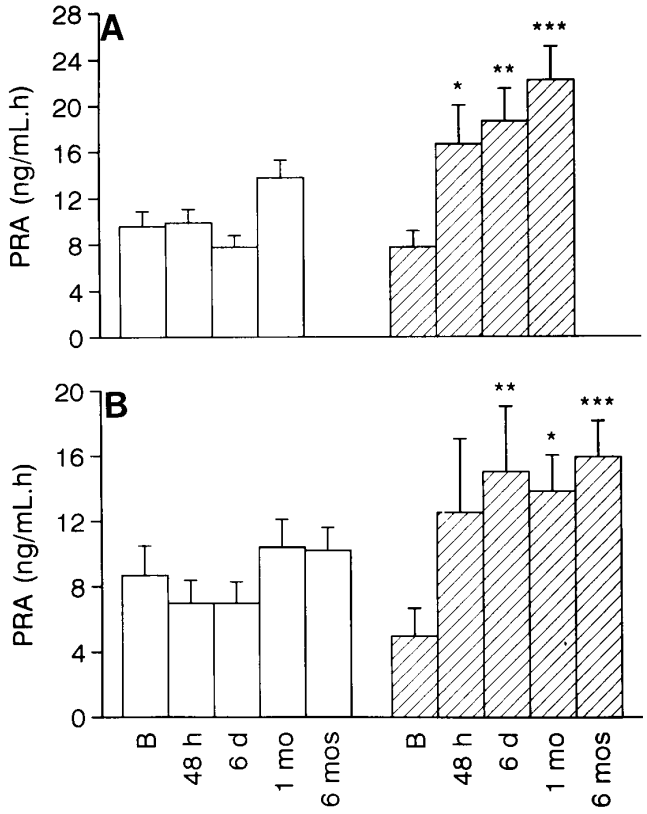

Figure 1. (*A* and *B*) PRA at baseline (B), 48 hours, 6 days, 1 month, and 6 months (shown in *B* only) after discharge in patients without (□) and with (▨) postparacentesis circulatory dysfunction. Data are presented as mean ± SEM. $*P < 0.02$, $**P < 0.001$, $***P < 0.0001$ vs. baseline.

former group (relative risk, 1.5; 95% confidence interval, 1.05–2.24) (Table 4). The effects of paracentesis on arterial pressure and laboratory parameters are shown in Table 5. Mean arterial pressure decreased significantly in the two groups. No significant changes were observed in hematocrit value. Serum creatinine level increased and serum sodium level decreased significantly only in patients who developed postparacentesis circulatory dysfunction. Mortality rate during the first hospital stay was very low in the two groups (Table 4).

During follow-up, patients who developed postparacentesis circulatory dysfunction had a significantly higher probability of being readmitted to the hospital than those who did not develop it (median time to first readmission, 1.3 and 3.5 months, respectively). This was caused by a higher probability of being readmitted for ascites (median time to first readmission for ascites, 5.2 vs. 38.8 months, respectively; Figure 2) because the probability of being readmitted for other causes was similar. The mean need for diuretics during follow-up was significantly higher ($P < 0.02$) in patients developing postparacentesis circulatory dysfunction (furosemide, 69 ± 54 mg/day; spironolactone, 213 ± 96 mg/day) than in those who did not (45 ± 48 and 130 ± 95 mg/day, respectively). Moreover, the development of circulatory dysfunction after paracentesis was associated with a shorter survival rate (Figure 3). Causes of death in patients who did not develop postparacentesis circulatory dysfunction were liver failure (39 patients), gastrointestinal bleeding (23 patients), bacterial infection (11 patients), and other (5 patients); in patients developing the condition, they were liver failure (18 cases), gastrointestinal bleeding (16 cases), bacterial infection (9 cases), and other (2 cases).

Predictive Factors of Postparacentesis Circulatory Dysfunction and Survival

To seek variables associated with an increased risk of postparacentesis circulatory dysfunction, 18 parameters (including demographic and clinical data, existence of peripheral edema, liver and renal function tests, arterial pressure, Child–Pugh score, PRA [see Table 1], liters of ascites removed, and type of plasma expander used) were analyzed for predictive value in a univariate and multivariate analysis. Only the volume of ascites removed (8.9 ± 3.5 vs. 7.2 ± 2.6 L in patients who did and did not develop postparacentesis circulatory dysfunction, respectively; $P = 0.0001$) and the type of the plasma expander (see Table 2) had predictive value in the univariate as well as in the multivariate analysis (regression coefficient, −0.1799 [$P = 0.0001$] and −0.8664 [$P = 0.005$], respectively). The importance of these factors is further emphasized in Figure 4, which shows the incidence of postparacentesis circulatory dysfunction in the whole series of patients grouped according to the volume of ascites removed and the type of plasma expander used.

Table 4. Number and Types of Complications During First Hospitalization in Patients Who Did (Group A) and Did Not (Group B) Develop Postparacentesis Circulatory Dysfunction

	Group A (n = 85)	Group B (n = 195)
Duration (*days*)	16 ± 10	16 ± 33
No. of patients with complications (%)	30 (35)	49 (25)
No. of complications	37	49
Hyponatremia (%)[a]	22 (26)	30 (15)
Renal impairment (%)	8 (9)	16 (8)
Hepatic encephalopathy (%)	3 (3)	9 (5)
Gastrointestinal bleeding (%)	2 (2)	3 (1)
Bacterial infection (%)	1 (1)	9 (5)
Other (%)	1 (1)	0 (0)
No. of patients who died (%)	5 (6)	6 (3)

[a] $P = 0.04$.

Table 5. Arterial Pressure and Laboratory Parameters Before and 6 Days After Paracentesis in Patients Who Did (Group A) and Did Not (Group B) Develop Postparacentesis Circulatory Dysfunction

Variable	Group A		Group B	
	Before	6 days after	Before	6 days after
Mean arterial pressure (*mm Hg*)	82 ± 10	79 ± 10[a]	84 ± 12	80 ± 11[b]
Hematocrit (*%*)	33 ± 6	33 ± 6	32 ± 6	32 ± 6
Serum creatinine (*mg/dL*)	0.89 ± 0.3	1.03 ± 0.4[b]	0.96 ± 0.4	0.99 ± 0.6
Serum sodium (*mEq/L*)	132 ± 6	130 ± 7[b]	133 ± 6	133 ± 6
PRA ($ng \cdot mL^{-1} \cdot h^{-1}$)	8.0 ± 7.3	18.6 ± 14.8[b]	9.3 ± 11.5	8.0 ± 9.8[b]

[a]$P < 0.01$, [b]$P < 0.001$ vs. baseline values.

Significant differences between patients receiving albumin and those receiving dextran 70 or polygeline were observed only when the volume of ascites removed was >5 L.

In a univariate analysis, six laboratory variables (PRA, concentrations of bilirubin, albumin, creatinine, and sodium in the serum, and prothrombin time), renal failure, and Child–Pugh score at inclusion, and the development of postparacentesis circulatory dysfunction (Figure 3) were significantly related with survival. However, only four were found to be independent predictors of survival in the multivariate analysis, including serum sodium, Child–Pugh score, serum creatinine, and postparacentesis circulatory dysfunction (regression coefficients, −0.0599, 0.1934, 0.5768, and 0.4123, respectively; *P* values equal 0.000, 0.010, 0.010, and 0.039, respectively).

Discussion

The hemodynamic and neurohumoral changes that occur after large-volume paracentesis without plasma volume expansion have been investigated in detail.[10–15,22–26] Within the first 12 hours after paracentesis, there is an improvement in circulatory function characterized by an increase in cardiac output and stroke volume, a reduction in cardiopulmonary pressures, and a deactivation of vasoconstrictor and antinatriuretic systems (i.e., the renin-angiotensin and the sympathetic nervous system). This early phase is followed by opposite hemodynamic changes with reduction in cardiac output and marked activation of vasoconstrictor systems. Renal function improves during the first hours after paracentesis and worsens 24–48 hours after the proce-

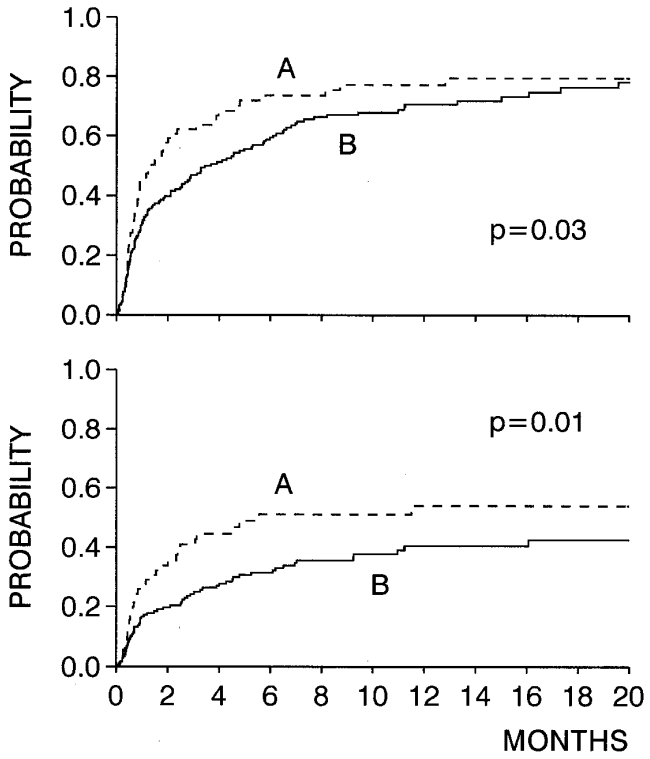

Figure 2. Probability of readmission to the hospital during follow-up for any complication (*top*) or ascites (*bottom*) in patients who (A) did and (B) did not develop postparacentesis circulatory dysfunction.

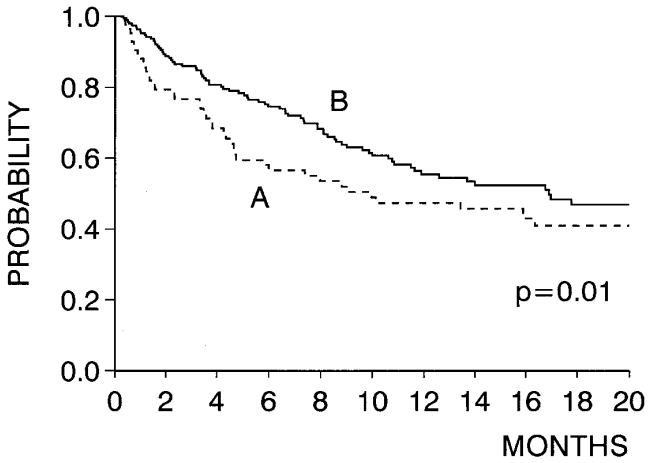

Figure 3. Probability of survival after entry into the study in the patients who (A) did and (B) did not develop postparacentesis circulatory dysfunction.

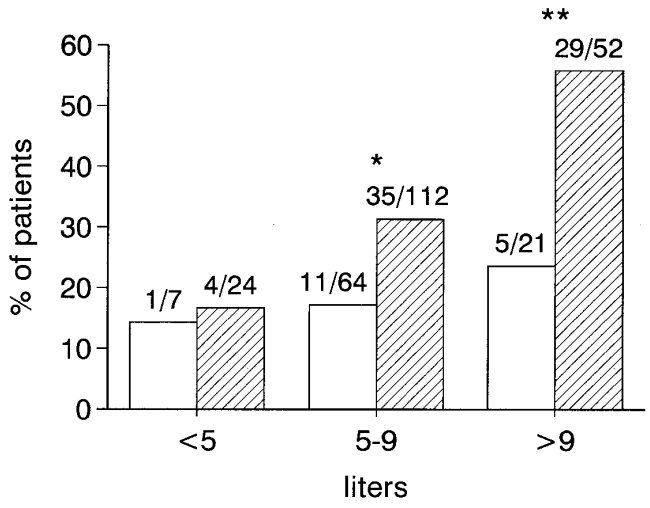

Figure 4. Incidence of postparacentesis circulatory dysfunction according to the plasma expander used (albumin, □; dextran 70 or polygeline, ▨) and the volume of ascitic fluid drained. $*P = 0.04$ and $**P = 0.02$ with respect to the incidence in patients receiving albumin. Figures represent patients developing postparacentesis circulatory dysfunction and patients at risk, respectively.

dure.[10,12,15,23,25] The recommendation of the use of albumin as plasma expander after paracentesis is based on findings showing that albumin maintains the initial improvement in circulatory function after paracentesis and prevents the subsequent activation of vasoconstrictor systems and impairment in renal function.[10,15] The mechanism of the circulatory dysfunction after paracentesis remains incompletely understood. Plasma volume and hematocrit do not change in patients developing circulatory dysfunction after paracentesis, indicating that there is no reduction in total intravascular volume.[27] The existence of marked activation of vasoconstrictor systems without changes in plasma volume therefore suggests a reduction in effective intravascular volume after paracentesis. The observation that these neurohumoral changes are associated with a decrease in systemic vascular resistance suggests that the circulatory dysfunction is caused by an accentuation of the arterial vasodilatation of cirrhotic patients.[28]

The present study was designed to investigate whether circulatory dysfunction after paracentesis has any impact on the clinical course of the disease and assess the effectiveness of plasma expanders different from albumin in the prevention of this abnormality.

A major finding was that postparacentesis circulatory dysfunction is not spontaneously reversible but persists during follow-up. More importantly, this disorder is associated with faster reaccumulation of ascites and impaired prognosis. Because circulatory disturbance after paracentesis is characterized by marked activation of antinatriuretic systems, the faster reaccumulation of ascites in these patients was probably related to an accentuation of renal sodium retention. This contention is further supported by the increased diuretic requirements in this group of patients. The reason for the impaired prognosis is more difficult to ascertain. Perhaps postparacentesis circulatory dysfunction developed in patients with more advanced disease. However, this possibility is unlikely because patients in whom circulatory dysfunction developed after paracentesis did not differ from those in whom the disturbance did not develop in the degree of impairment of liver and renal function or severity of alterations in systemic hemodynamics. A more plausible explanation for the impaired prognosis of patients developing postparacentesis circulatory dysfunction is that changes in neurohumoral systems caused an acceleration of the course of the disease. Theoretical basis supports this possibility. First, it is well known that spontaneous impairment in systemic and renal circulatory function in cirrhotic patients with ascites is associated with a poor prognosis.[29,30] Second, angiotensin II and other vasoactive substances released during postparacentesis circulatory dysfunction, such as norepinephrine, are powerful renal vasoconstrictors. On the other hand, plasma levels of atrial natriuretic peptide, a vasodilator hormone that participates in the maintenance of renal perfusion in cirrhosis,[31] decrease in patients developing circulatory dysfunction after paracentesis.[12,14,15] This imbalance between renal vasoactive systems may accelerate the impairment of renal circulatory function and favor the development of renal dysfunction.[32] Finally, angiotensin II and norepinephrine increase intrahepatic vascular resistance and reduce hepatic blood flow.[33] The neurohormonal changes associated with postparacentesis circulatory dysfunction may therefore aggravate portal hypertension and impair hepatic function. Nevertheless, because it is possible that the impaired prognosis in patients with postparacentesis circulatory dysfunction is related to some unrecognized factor(s), further studies are clearly needed to investigate this feature. Whatever the reason for the relationship between postparacentesis circulatory dysfunction and impaired survival, this observation is a very strong argument for the use of measures to prevent this phenomenon.

The development of circulatory dysfunction after paracentesis was clinically silent. Neither changes in arterial pressure or laboratory parameters nor the development of complications during hospitalization were useful to diagnose the development of circulatory dysfunction (Tables 4 and 5). Measurement of PRA 2 days after treatment, although very specific, had a low sensitivity.

Another important observation of this study was that

circulatory dysfunction after paracentesis was better prevented by albumin than by dextran 70 or polygeline. The type of plasma expander and the volume of ascites removed were the only independent predictors of postparacentesis circulatory dysfunction identified in our study. When the volume of ascites removed was <5 L, a similar incidence was observed in patients treated with albumin and in those receiving dextran 70 or polygeline (14.2% and 16.6%, respectively). These percentages are comparable with the 11.6% incidence of spontaneous deterioration in circulatory function observed within the first week of hospitalization in 43 untreated cirrhotic patients with ascites (V. Arroyo, unpublished observation), suggesting that postparacentesis circulatory dysfunction is very uncommon when relatively small volumes of ascitic fluid are removed. In contrast, when the volume of ascites drained was >5 L, the incidence of postparacentesis circulatory dysfunction increased markedly and in parallel with the amount of the ascitic fluid removed only in patients treated with dextran 70 or polygeline (31.2% and 55.7% when the volume of the ascites drained was 5–9 L and >9 L, respectively) (Figure 4). These data suggest that albumin almost totally prevents the development of circulatory dysfunction after paracentesis regardless of the volume of ascites removed and indicate that albumin is the plasma expander of choice in cirrhotic patients in whom the amount of ascitic fluid drained is >5 L. In patients treated with small-volume paracentesis, albumin can be substituted with the less expensive synthetic plasma expanders dextran 70 or polygeline. The reason why albumin is more effective than dextran 70 and polygeline in the prevention of postparacentesis circulatory dysfunction is probably related to the longer intravascular persistence of albumin than of the artificial colloids. In fact, the half-life of artificial colloids is <24 hours (5 hours for polygeline and 12–24 hours for dextran 70),[34,35] whereas the half-life of albumin in patients with cirrhosis is approximately 21 days.[36,37]

Despite a lower incidence of postparacentesis circulatory dysfunction, patients treated with albumin did not show significant differences in the incidence of complications during follow-up or survival compared with patients treated with dextran 70 or polygeline. Possibly the 16%–20% difference in the incidence of postparacentesis circulatory dysfunction in albumin vs. nonalbumin groups was relatively small to translate into significant differences in these parameters for the sample size of the study.

In conclusion, the current study shows that postparacentesis circulatory dysfunction is not spontaneously reversible and is associated with an increased probability of ascites recurrence and reduced survival. Albumin is more effective than dextran 70 and polygeline in the prevention of this abnormality and should be considered the plasma expander of choice in patients in whom more than 5 L of ascitic fluid are removed.

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