Liver, Pancreas and Biliary Tract

Prevention of paracentesis-induced circulatory dysfunction in cirrhosis: Standard vs half albumin doses. A prospective, randomized, unblinded pilot study

Carlo Alessandria*, Chiara Elia, Lavinia Mezzabotta, Alessandro Risso, Alida Andrealli, Maurizio Spandre, Anna Morgano, Alfredo Marzano, Mario Rizzetto

Division of Gastroenterology and Hepatology, San Giovanni Battista Hospital – University of Turin, Turin, Italy

1. Introduction

Total paracentesis is the first-line therapy for refractory ascites in patients with cirrhosis [1,2] and it has been shown to be as effective as standard therapy with diuretics in the management of tense ascites, with significantly faster resolution and lower rate of complications [3,4]. Paracentesis-induced circulatory dysfunction (PIDC), a disorder characterized by marked activation of the renin–angiotensin axis secondary to the further increase of an already established arteriolar vasodilatation [5], is a frequent and potentially harmful complication of large volume paracentesis [6]. It is associated with faster reaccumulation of ascites, renal impairment and shorter survival [6]. The causes of this syndrome are probably multiple and still not completely known. Dynamics of paracentesis (the rate of fluid extraction) [5,7], mechanical modifications (due to abdominal decompression) [7,8] and release of vasodilator molecules, such as nitric oxide, from vascular endothelium are thought to play a major role in development of PIDC [5].

PIDC appears in up to 80% of patients who are not infused with plasma expanders after large volume paracentesis (LVP); plasma volume expansion after paracentesis strongly reduces the incidence of PIDC [9].

A controversial issue remains the kind of volume replacement that should be given. Albumin is the most used plasma expander; its safety and efficacy in preventing PIDC is well demonstrated, as it reduces the rate of development of PIDC to about 15% [3,6,9]. However, costs and limited availability have prompted to the research of alternatives. Many other options were tested, including different plasma expanders (haemaccel [10], dextran-70 [6,11], polygeline [6], dextran-40 [12], saline [13]) and vasoconstrictor agents (terlipressin [14,15], noradrenalin [16], midodrine alone [17,18] or combined with octreotide [19]); however, lower efficacy with respect to albumin infusion [6,10–13], high costs [14,15], potential harmfulness [16] and controversial results [17–19] have made...
albumin the plasma-expander of choice. It is recommended that the albumin infusion consists of 8 g/L of ascites removed [1,2,20], but there is no study comparing different doses of albumin in this context.

The aim of this study was to compare standard (8 g/L of ascites removed) vs half (4 g/L of ascites removed) albumin doses in the prevention of PICD in patients with cirrhosis and ascites treated by large volume paracentesis.

2. Patients and methods

This prospective study was conducted in the Gastro-Hepatology Unit of our hospital between January 2004 and December 2008. During this five-year period all consecutive cirrhotic patients with tense ascites were investigated for inclusion. The diagnosis of cirrhosis was based on clinical, laboratory and ultrasonographic findings. Inclusion criteria were: cirrhosis with tense ascites submitted to paracentesis >5 L; age between 18 and 75 years; written informed consent. Exclusion criteria were: multinodular hepato-cellular carcinoma (>3 nodules), portal vein thrombosis, ongoing bacterial infection, ongoing or recent (less than one week) bleeding, cardio-pulmonary failure, serum creatinine >2 mg/dL (176 μmol/L), intrinsic renal disease, ongoing treatment with vasoactive drugs (including beta-blockers), recent use (within 30 days) of plasma expanders.

Patients were on low sodium diet (60–80 mEq/day) without diuretic therapy for at least 3 days before paracentesis. On day 3 blood and 24-h urine samples were obtained for haematologic and biochemical studies. Patients were in a bed rest supine position for at least 45 min before blood samples were taken. Samples were immediately brought to the laboratory and centrifuged. The plasma obtained was frozen (−80 °C) until analysis.

Then a total paracentesis (>5 L) was performed under strict sterile conditions as previously described [1]. Leukocytes count and percentage of polymorphonuclear leukocytes were determined in ascitic fluid.

All patients were given intravenous albumin (Uman Albumin 20 g of albumin/100 mL; Kedrion S.p.A., Barga, Lucca, Italy) within the first hour after the procedure. Patients were randomly assigned to treatment with albumin 4 g (group 1) or albumin 8 g (group 2) per litre of ascites removed by paracentesis. Randomization was made by using the sealed opaque envelopes method. Patients with serum creatinine between 1.5 and 2 mg/dL were randomized independently from those with serum creatinine below 1.5 mg/dL to ensure a similar number of cases with renal failure in both groups.

Patients did not receive diuretics during the 6 days following paracentesis. At day 6 from paracentesis, blood and 24-h urine samples were newly obtained for biochemical tests, including plasma renin activity and plasma aldosterone, following the same procedure previously defined.

After day 6 from paracentesis diuretics were reintroduced as needed and patients then discharged from hospital when medically fit. Patients were followed-up for 6 months or until transjugular intrahepatic portosystemic shunt (TIPS), liver transplantation or death. During follow-up patients were treated with diuretics and large volume paracentesis followed by albumin infusions at standard doses as needed. Patients with no or small varices did not receive any kind of prophylactic treatment. Patients with medium or large varices and without any kind of prevention at inclusion were treated with propranolol after day 6 from paracentesis and continued this drug during the follow-up. Patients with contraindications to beta-blockers were treated with band ligation.

The study protocol conformed to the ethical guidelines of the 1975 Helsinki declaration.

The study was approved by the local Investigation Committee and written, informed consent was obtained from all patients.

3. Methods of measurement

Plasma renin activity and plasma aldosterone levels were measured by radioimmunoassay [21]. The normal values for PRA and plasma aldosterone in our laboratory are 0.1–4 ng/mL/h and 12–150 pg/mL, respectively.

4. Statistical analysis

The main end point of the study chosen to calculate the sample size was the incidence of paracentesis-induced circulatory dysfunction. Because there are no data on the incidence of PICD after paracentesis and infusion of albumin 4 g/L of ascites removed, following the example of a previously published study [13] the sample size was calculated according to the study of Planas et al. [11], which showed an incidence of PICD of 15% when patients were treated with albumin 8 g/L of ascites removed. Expecting no difference in the proportion of PICD after the infusion of albumin 4 g/L of ascites removed, we calculated that with 35 patients per group the 95% confidence interval of the difference would be between ±17%.

Comparisons between the two groups were performed using the Student’s t-test for continuous data and the χ² and Fisher test for categorical data. Comparisons of the variables in the same group were performed using the Wilcoxon test and the χ² and Fisher test.

To identify variables predicting the development of PICD we performed an univariate analysis by χ² test and Student’s t test. Variables were then introduced in a multivariate analysis using a stepwise logistic regression model to identify independent predictors of development of PICD.

Survival curves were calculated by the Kaplan–Meier method and compared with the log rank test. Patients submitted to TIPS or liver transplantation during the follow-up were considered censored at the time of the procedures.

Statistical analyses of the data were performed by using SPSS Statistical Software (SPSS Inc., Chicago, IL). Results are expressed as mean ± standard deviation. All p-values are 2 tailed, with values less than .05 considered statistically significant.

5. Definitions

5.1. Paracentesis-induced circulatory dysfunction

Increase in PRA of more than 50% of the preparacentesis value to a level more than 4 ng/mL/h on the 6th day after paracentesis [6].

5.2. Renal failure

Increase in serum creatinine >50% compared with the baseline value to a level >1.5 mg/dL (132 μmol/L) on the 6th day after paracentesis [9]. Patients with a serum creatinine level >1.5 mg/dL (132 μmol/L) at the inclusion in the study who showed an increase in serum creatinine >30% compared with the baseline values on the 6th day after paracentesis were also considered as patients developing renal failure.

5.3. Hyponatremia

Decrease in serum sodium ≥5 mEq/L to a level <130 mEq/L on the 6th day after paracentesis. Patients with a serum sodium level <130 mEq/L at the inclusion in the study who showed a decrease
in serum sodium \( \geq 5 \text{ mEq/L} \) on the 6th day after paracentesis were also considered as patients developing hyponatremia [9].

6. Results

During the study period 180 consecutive patients with cirrhosis who were admitted to the hospital for tense ascites were investigated for inclusion (Fig. 1).

One hundred and ten patients were not considered eligible for: ongoing therapy with beta-blockers for the prevention of variceal bleeding (29 patients, 16%), advanced hepatocellular carcinoma (25 patients, 14%), spontaneous bacterial peritonitis (SBP, 18 patients, 10%) or other bacterial infections (5 patients, 3%), of portal vein thrombosis (13 patients, 7%), serum creatinine levels above 2 mg/dL (10 patients, 6%), gastrointestinal bleeding (2 patients, 1%), significant intrinsic renal disease (8 patients, 4%). The remaining 70 patients did not show any of the exclusion criteria, gave informed written consent and were then enrolled in the study. They were randomly assigned to treatment with albumin 4 g/L of ascites removed by paracentesis (35 patients; group 1) or albumin 8 g/L of ascites removed (35 patients; group 2); they all received the allocated intervention. No patient was lost at follow-up. The final analysis of the trial included all the 70 patients.

6.1. Characteristics at inclusion and data related to paracentesis

6.1.1. Characteristics at inclusion

Table 1 shows the characteristics of patients at study inclusion. No significant differences were detected between the two groups regarding clinical data, liver and renal function tests, mean arterial pressure, plasma renin activity and plasma aldosterone.

6.1.2. Data related to paracentesis

The volume of ascites removed was 7.4 ± 3.1 L (median: 8 L; range 5.2–19 L) and 8 ± 3.7 L (median: 7.8 L; range: 5.4–16 L) in group 1 and 2, respectively (\( p = \text{ns} \)). The amount of albumin infused was significantly higher in group 2 than in group 1 according to the schedule (64.2 ± 23 vs 28.1 ± 14 g; \( p < 0.0001 \)). As an indi-

![Fig. 1. Flow diagram of the study, with allocation to treatment and follow-up.](image)

### Table 1

Demographic, clinical and laboratory data of all patients according to the group of treatment at the time of inclusion.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (4 g/L)</th>
<th>Group 2 (8 g/L)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 ± 12</td>
<td>57 ± 11</td>
<td>0.8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>30/5</td>
<td>27/8</td>
<td>0.5</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>34%</td>
<td>40%</td>
<td>0.8</td>
</tr>
<tr>
<td>N. with renal insufficiency*</td>
<td>3</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Plasma aldosterone (pg/mL)</td>
<td>197 ± 51</td>
<td>130 ± 31</td>
<td>0.3</td>
</tr>
</tbody>
</table>

MELD: model for end-stage liver disease. Renal insufficiency was defined as serum creatinine level greater than 1.5 mg/dL (132 µmol/L). * Hyponatremia was defined as serum sodium level less than 130 mEq/L.

rect index of reaccumulation of ascites, body weight was recorded immediately after paracentesis and 6 days after paracentesis. The increment of weight at day 6 was 2 ± 2.5 kg in group 1 and 2, respectively (\( p = \text{ns} \)). The mean cost of the administered albumin per paracentesis was 105 ± 42 Euros in group 1 and 227 ± 38 Euros in group 2, \( p < 0.0001 \). Duration of hospitalization (from randomization to discharge from hospital) was also similar in both groups (group 1, 9.4 ± 6 days; group 2, 8.6 ± 9 days; \( p = \text{ns} \)).

Table 2 shows the systemic haemodynamic and laboratory variables before paracentesis as well as 6 days after the procedure. No significant variations in mean arterial pressure, activation of the renin–angiotensin–aldosterone and sympathetic nervous systems, serum sodium and serum creatinine levels were observed in either group.

6.1.3. Complications

Table 3 shows the complications observed during the study period (from paracentesis to day 6). Five of the 35 patients (14%) in
group 1 and 7 of the 35 patients (20%) in group 2 developed PICD (p = ns). The number of complications other than PICD was similar between the two groups. Three patients of group 1 (3/35, 9%) and 2 patients of group 2 (2/35, 6%) developed hyponatremia (p = ns). No patient developed renal failure. We did not observe any episode of gastrointestinal bleeding or hepatic encephalopathy.

In group 1, amongst the 5 patients who developed PICD none developed hyponatremia (none of the 3 patients who developed hyponatremia showed PRA levels variations consistent with the diagnosis of PICD). In group 2, amongst the 7 patients with PICD only one developed hyponatremia. No patient died during the 6-day study period.

6.1.5.3. Hospital readmissions. The number of hospital readmissions related to complications of cirrhosis and portal hypertension was similar: 12 in group 1 (8 for tense ascites and 4 for hepatic encephalopathy) and 14 in group 2 (9 for tense ascites, 4 for hepatic encephalopathy and 1 for bleeding related to congestive gastropathy).

6.1.5.4. Survival. Six patients died during the follow-up, 3 in each group. In 4 patients (2 in each group) liver failure was the main cause of death. The remaining 2 patients (1 in each group) died for septic shock (due to Escherichia coli urinary tract infection in group 1 and to culture-negative spontaneous bacterial peritonitis in group 2). Amongst the remaining patients, 3 were transplanted (2 in group 1 and 1 in group 2) and 2 underwent TIPS (1 in each group). Patients were censored at the time of the procedures. Survival at 6 months (Fig. 2) was not significantly different between group 1 (mean 148 ± 49 days) and group 2 (mean 158 ± 56 days; p = ns).

6.1.5.5. Beta-blockers vs non beta-blockers group. No differences were found between patients who were and patients who were not under beta-blockers. Amongst the 26 hospital readmissions, 17 were observed in patients under beta-blockers (17/45, 38%) and 9 in patients without beta-blockers (9/25, 36% (p = ns). Similarly, amongst the six patients who died, 4 were under beta-blockers (4/45, 9%) and 2 were not (2/25, 8%; p = ns).

6.1.5.6. Global costs. No significant differences were found regarding the hospital costs. According to the Diagnosis Related Groups system the costs for the hospital readmissions were 53,168 Euros in group 1 (12 readmissions, mean cost for readmission: 4,430 ± 380 Euros) and 60,729 Euros in group 2 (14 readmissions, mean cost for readmission: 4,338 ± 456 Euros); p = ns.
7. Discussion

Paracentesis-induced circulatory dysfunction develops in up to 80% of cirrhotic patients with tense ascites treated by large volume paracentesis if this is not followed by plasma volume expansion [9].

The development of PICD was associated with worsening of renal function, reaccumulation of ascites, portal pressure increase [6,22] and diminished survival [6,23].

Intravenous albumin infusion is effective in avoiding complications of paracentesis [9]; PICD development rate is reduced down to about 15% [6,9]. Other plasma volume expanders were tested (synthetic colloids, saline solution), but they were less effective than albumin in the prevention of PICD [6,10–13].

The recommended dose of albumin is 8 g/L of ascites evacuated. This schedule, proposed almost twenty years ago [3,20] to best replace the amount of proteins removed with the ascitic fluid, still remains a landmark in paracentesis [1,2]. It was calculated on the basis of mean ascitic volume removed per tap and mean protein concentration in ascitic fluid in a series of cirrhotic patients (3). However, following this schedule a high albumin amount is needed, with remarkable costs.

To our knowledge no study was performed to compare the efficacy of different doses of albumin in this context and ours is the first randomized, controlled investigation comparing standard vs reduced doses of albumin in the prevention of PICD. The dose of 4 g of albumin for litre of ascites removed was chosen arbitrarily to halve the cost of treatment, as a first step towards the definition of the best cost saving schedule to be used in this setting.

At inclusion, no significant differences were detected between patients treated with albumin 4 g/L of ascites removed and patients treated with albumin 8 g/L of ascites removed regarding clinical data, standard liver and renal function tests, and systemic haemodynamics. The volume of ascitic fluid removed was similar. Thus, the two groups were comparable in terms of liver failure, renal and circulatory dysfunction and amount of fluid removed by paracentesis.

PICD was prevented in most patients. The incidence of PICD during hospitalization was not statistically different between group 1 (5/35 patients, 14%) and group 2 (7/35 patients, 20%) and was similar to the rate of PICD reported in published studies that made use of albumin infusion at the recommended dose [6,9]. However, the cost of the administered albumin per paracentesis was markedly reduced in group 1 (105 ± 42 Euros) compared to group 2 (227 ± 38 Euros). These data suggest that half doses of albumin are effective in the prevention of PICD in cirrhotics, but at a distinctly diminished cost.

After 6 days from paracentesis the effects on systemic haemodynamic and laboratory variables were similar in the two groups. Prevention of paracentesis-induced vasodilatation explains the lack of changes in effective circulating volume and in renal function in both groups.

In patients receiving adequate plasma volume expansion after large volume paracentesis, the reported incidence of development of renal failure and of hyponatraemia is low (5–15%) [6,9,13–15]. In keeping with these data, 3 patients of group 1 (9%) and 2 patients of group 2 (6%) developed hyponatraemia and none experienced renal failure. We observed a poor correlation between the development of hyponatraemia and PICD. This apparently surprising finding is, nevertheless, consistent with the literature [13] and may reflect the fact that only a small proportion of patients with PICD develops alterations of serum electrolytes [6,13] and that, on the contrary, a spontaneous development of hyponatraemia is often seen in cirrhotic patients with ascites, independently from PICD.

Of interest, our results confirm that variables estimating systemic haemodynamics are very important in cirrhotic patients with ascites [24], the mean arterial pressure representing the most reliable variable in predicting the development of PICD in our study.

It should be said that it is possible that some patients would have required different amounts of albumin to be infused if we had
calculated them on the basis of albumin and proteins evacuated by paracentesis. This kind of approach would be very interesting and should be investigated.

Finally, a follow-up evaluation of 6 months showed that the rate of survival and of recurrence of ascites and complications due to portal hypertension requiring readmissions to hospital were not different between the two groups. These data strengthen our results, allowing to perform a rationale comparison of the effectiveness of the two treatments and of the global cost of the management of these patients.

We are aware that our study has flaws that somewhat limit its value. The sample size is clearly low to demonstrate the equivalence of the two treatments or the non-inferiority of the low dose albumin schedule compared to the standard dose of albumin. Such a study would require more than 100 patients per group.

Furthermore, our patients, although presenting with end-stage liver disease and tense ascites, were not so compromised in terms of circulatory and renal dysfunction. Consequently it must be underlined that half doses of albumin seem to be effective in the prevention of PICD in cirrhotics with stable clinical conditions and relatively preserved cardiovascular function, whereas patients with severe circulatory dysfunction and/or ongoing clinical decompensations would maybe require the standard doses of albumin. Therefore, the application of our results to more compromised patients requires further investigations.

Taking into account all these defects we still think that our study deserves consideration. It introduces an important element of novelty as it explores a new approach to reduce the cost of expansion with albumin. Furthermore, although the sample size was frankly admitted to be low to demonstrate the equivalence of the two schedules or the non-inferiority of the experimental treatment compared to the standard one, differences and confidence intervals of PICD rates and its related complications (Table 3) suggest an effectiveness of the experimental arm with low albumin doses.

In conclusion, the results of this unblinded, randomized, pilot study suggest that treatment with half doses of albumin is effective and safe in the prevention of PICD and of its related clinical complications in cirrhotic patients with tense ascites treated by LVP, but with a significant cost reduction. These findings should be considered as the first step in the investigation of the best cost saving schedule of albumin to be used in cirrhotic patients after large volume paracentesis and cannot be currently used to generate formal recommendations. Larger appropriately powered equivalence or non-inferiority studies are mandatory to confirm these results.

Financial disclosure

None declared.

Conflict of interest statement

None declared.

List of abbreviations

LVP, large volume paracentesis; PICD, paracentesis-induced circulatory dysfunction; PRA, plasma renin activity; SBP, spontaneous bacterial peritonitis.

Acknowledgement

Supported by: Azienda Ospedaliero-Universitaria San Giovanni Battista di Torino.

References