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

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ABSTRACT

Background: Paracentesis-induced circulatory dysfunction is a well-known complication of large volume paracentesis. Albumin infusion (8 g of albumin/L of ascites removed) is effective in preventing it, but high costs and scant availability limit its use.
Aim: To compare standard vs half albumin doses.
Methods: Seventy cirrhotic patients treated with large volume paracentesis were randomized to receive intravenous albumin as prevention of paracentesis-induced circulatory dysfunction: group 1 (35 patients) received 4 g/L of ascites removed, group 2 (35 patients) received 8 g/L of ascites removed.
Results: The incidence of paracentesis-induced circulatory dysfunction (14% vs 20% in group 1 and group 2, respectively; p = ns), hyponatremia (9% vs 6%, p = ns) and renal impairment (0% in both groups) on the 6th day from paracentesis was similar between the two groups. After 6 months of follow-up, rates of survival and of recurrence of ascites requiring large volume paracentesis were not different between the two groups.
Conclusions: This unblinded, randomized, pilot study suggests that treatment with half doses of albumin is effective in the prevention of paracentesis-induced circulatory dysfunction and its related clinical complications in cirrhotic patients with tense ascites treated by large volume paracentesis. If confirmed, these results could support a significant costs reduction in the management of ascites in cirrhotic patients.

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 (PICD), 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 PICD [5].

PICD 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 PICD is well demonstrated, as it reduces the rate of development of PICD 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

☆ The clinical trial was registered with the U.S. National Institute of Health database (NCT00428506).

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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 hepatocellular 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 χ^2 and Fisher test for categorical data. Comparisons of the variables in the same group were performed using the Wilcoxon test and the χ^2 and Fisher test.

To identify variables predicting the development of PICD we performed an univariate analysis by χ^2 test and Student's 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