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Terlipressin and Albumin vs Albumin in Patients With Cirrhosis and Hepatorenal Syndrome: A Randomized Study

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Background & Aims: **Hepatorenal syndrome is common in patients with advanced cirrhosis and constitutes a major problem in liver transplantation. There is no effective medical treatment for hepatorenal syndrome.** ***Methods:*** **Forty-six patients with cirrhosis and hepatorenal syndrome, hospitalized in a tertiary care center, were randomly assigned to receive either terlipressin (1–2 mg/4 hour, intravenously), a vasopressin analogue, and albumin (1 g/kg followed by 20–40 g/day) (n = 23) or albumin alone (n = 23) for a maximum of 15 days. Primary outcomes were improvement of renal function and survival at 3 months.** ***Results:*** **Improvement of renal function occurred in 10 patients (43.5%) treated with terlipressin and albumin compared with 2 patients (8.7%) treated with albumin alone ($P = .017$). Independent predictive factors of improvement of renal function were baseline urine volume, serum creatinine and leukocyte count, and treatment with terlipressin and albumin. Survival at 3 months was not significantly different between the 2 groups (terlipressin and albumin: 27% vs albumin 19%, $P = .7$). Independent predictive factors of 3-month survival were baseline model for end-stage liver disease score and improvement of renal function. Cardiovascular complications occurred in 4 patients treated with albumin alone and in 10 patients treated with terlipressin and albumin, yet permanent terlipressin withdrawal was required in only 3 cases.** ***Conclusions:*** **As compared with albumin, treatment with terlipressin and albumin is effective in improving renal function in patients with cirrhosis and hepatorenal syndrome. Further studies with large sample sizes should be performed to test whether the improvement of renal function translates into a survival benefit.**

Hepatorenal syndrome (HRS) is a characteristic form of renal failure that occurs in patients with advanced cirrhosis and is associated with a very poor outcome.[1,2] Because of the lack of effective therapies, HRS has become a major issue in clinical practice. Moreover, in patients who are candidates for liver transplantation, HRS is a common cause of death before transplantation and is associated with an increased morbidity and reduced survival after transplantation.[3–5] Therefore, there is a need for effective therapies in patients with cirrhosis and HRS.

HRS is the consequence of a severe vasoconstriction of the renal circulation that causes a marked reduction in renal blood flow and glomerular filtration rate.[1,2] All attempts to induce renal vasodilatation by the administration of vasodilator drugs have been unsuccessful.[6] It is currently considered that HRS is the final consequence of a marked vasodilation of the splanchnic circulation secondary to an increased production of vasodilators in the splanchnic bed. As a result, the effective arterial blood volume is severely reduced, and there is compensatory activation of major vasoconstrictor systems, which are responsible for renal vasoconstriction.[1,2,7,8] This pathogenic concept has modified the approach to therapy of HRS, and several studies have been reported assessing the efficacy of vasoconstrictors, particularly vasopressin analogues to improve effective arterial blood volume.[9–14] These studies show that vasopressin analogues improve renal function in patients with HRS. However, the available information is limited because studies are either retrospective, have a small number of patients, or are not randomized. Therefore, the current study was undertaken to evaluate the effects of terlipressin on renal function and survival of patients with cirrhosis and HRS.

Patients and Methods

Study Population

A total of 67 consecutive patients with cirrhosis and HRS diagnosed between January 2002 and February

Abbreviations used in this paper: HRS, hepatorenal syndrome.

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2006 in 9 university hospitals were evaluated for inclusion in the study. The study was approved by the investigational review board at each hospital, and patients or relatives gave written informed consent to participate. Inclusion criteria were as follows: (1) cirrhosis as diagnosed by liver biopsy or clinical, biochemical, ultrasound, and/or endoscopic findings; (2) HRS either type 1, as defined by previously established criteria,[1] or type 2 with a serum creatinine greater than 175 μmol/L; (3) age 18 to 75 years; (4) absence of bacterial infection associated with findings of systemic inflammatory response as diagnosed by the presence of at least 2 of the following criteria: body temperature $<36°C$ or $>38°C$, heart rate >90 beats/min, respiration rate >20/min, and white-cell count <4 or $>12 \times 10^6$/L or $>6\%$ of band forms[15]; patients with bacterial infections, however, could be included in the study if renal failure persisted after infection resolution; (5) the absence of cardiovascular diseases and any extrahepatic disease that could affect the short-term prognosis; (6) the absence of findings suggestive of organic nephropathy; and (7) the absence of advanced hepatocellular carcinoma.[16] Twenty-one of the 67 patients screened were not randomized for the following reasons: severe cardiovascular disease (n = 4), refusal to participate (n = 4), terminal condition (n = 4), advanced hepatocellular carcinoma (n = 3), sepsis (n = 2), and miscellaneous reasons (n = 4).

A total of 46 patients were randomly assigned to 1 of 2 groups: 23 to terlipressin plus albumin and 23 to albumin alone. Albumin was given in association with terlipressin because there is evidence that albumin improves the beneficial effects of terlipressin on HRS.[14] Randomization was centralized in the Hospital Clínic of Barcelona and was done with the use of sealed opaque envelopes containing the treatment assignments, which were based on random numbers generated by the STATA statistical package (Stata Corp. 1999, 7.0, College Station, TX). Patients with type 1 HRS were randomized independently from those with type 2 HRS. A chart flow of patients included in the study is provided in Figure 1. The study was registered in Clinicaltrials.gov with the number NCT00287664.

Study Protocol

Before randomization, all candidate patients entered a screening period during which causes of renal failure other than HRS were excluded using criteria defined elsewhere.[1,2] Diuretic agents were withheld during this period, and a trial of plasma expansion was given to rule out the existence of renal failure because of volume depletion. If after the screening period (median time, 3 days) renal failure persisted and patients met the criteria of inclusion, patients entered the study and were randomized to receive either terlipressin and albumin or albumin alone. Physical examination, chest -ray, and routine laboratory tests were performed in all patients before the initiation of therapy and at

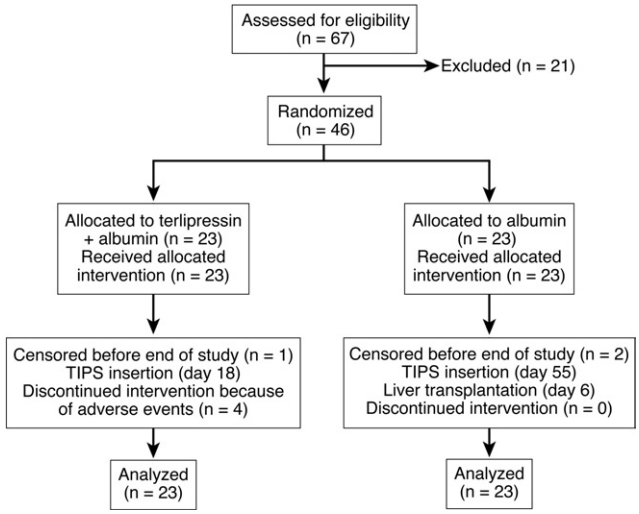

Figure 1. Flow chart of patients included in the study.

regular intervals during treatment. In all patients included, albumin (Albumin 20 percent; Instituto Grífols, Barcelona, Spain) was given at a dose of 1 gram per kilogram of body weight during the first 24 hours, followed by 40 grams per day, targeted to obtain a central venous pressure (CVP) between 10 and 15 cm of water. CVP was measured at least once a day throughout the study period. When CVP increased over 15 cm of water, the albumin dose was reduced to 20 g/day and was withheld when CVP increased above 18 cm of water or there were clinical or radiologic signs of pulmonary edema. In addition, these patients received intravenous (IV) boluses of furosemide. In patients randomized to treatment with terlipressin and albumin, terlipressin (Glypressin, Ferring AB, Sweden) was administered initially at a dose of 1 mg/4 hour as IV bolus for 3 days. If after the first 3 days serum creatinine had decreased at least 25% of the pretreatment values, the dose was not modified. In patients in whom serum creatinine had not decreased at least 25% of the pretreatment values within the first 3 days, the dose was increased to a maximum of 2 mg/4 hour. Terlipressin was given until serum creatinine had decreased below 133 μmol/L or for a maximum of 15 days. Terlipressin administration was withheld if patients developed signs or symptoms compatible with ischemic complications. An amendment was made during the study to allow treatment with terlipressin in patients assigned to albumin therapy who were potential candidates to liver transplantation if there was no improvement in renal function after 7 days. This amendment was requested by several institutional review boards on the basis of published studies reporting a reversal of HRS in patients treated with terlipressin.[11,12,14,17] Patients were admitted to the intensive care unit if they developed a severe complication of cirrhosis, had hemodynamic instability, or required ventilatory support. The majority of patients was hospitalized in a general hepatology ward. Complications of cirrhosis developing during the study in patients from both groups were treated according