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Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study☆

Tea Restuccia[1,2,3], Rolando Ortega[1,2,3], Monica Guevara[1,2,3], Pere Ginès[1,2,3,*], Carlo Alessandria[1,2,3], Osman Ozdogan[1,2,3], Miquel Navasa[1,2], Antoni Rimola[1,2], Juan Carlos Garcia-Valdecasas[4], Vicente Arroyo[1,2,3], Juan Rodés[1,2,3]

[1]*Liver Unit, Institute for Digestive Diseases, Hospital Clínic, University of Barcelona, Villarroel 170, Barcelona 08036, Catalunya, Spain*
[2]*Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS), Barcelona, Catalunya, Spain*
[3]*Instituto Reina Sofía de Investigación Nefrológica, Barcelona, Spain*
[4]*Department of Surgery, Institute for Digestive Diseases Hospital Clinic, Barcelona, Catalunya, Spain*

See Editorial, pages 159–161

***Background*: Pretransplant renal function is the major determinant of survival after liver transplantation (LTx). Patients with hepatorenal syndrome (HRS) have a poor outcome after LTx compared with patients transplanted without HRS.**

***Aim*: To analyze the impact of treatment of HRS before LTx on outcome after transplantation.**

***Methods*: The outcome of patients with HRS ($n = 9$) treated with vasopressin analogues before LTx was compared with that of a contemporary control group of patients without HRS ($n = 27$) matched by age, severity of liver failure, and type of immunosuppression.**

***Results*: Cases and controls were similar with respect to pretransplantation characteristics. Three-year survival probability was similar between the two groups (HRS-treated: 100% vs control: 83%, $P = 0.15$). No significant differences were found between the two groups with respect to the incidence of impairment of renal function after LTx (HRS-treated: 22% vs control: 30%), severe infections (22 vs 33%), acute rejection (33 vs 41%), days in Intensive Care Unit (6 ± 1 vs 8 ± 1), days in hospital (27 ± 4 vs 31 ± 4), and transfusion requirements (11 ± 3 vs 10 ± 2 units).**

***Conclusions*: Patients with HRS treated with vasopressin analogues before LTx have a posttransplantion outcome similar to that of patients transplanted with normal renal function. These results suggest that HRS should be treated before LTx.**

***Keywords*: Hepatorenal syndrome; Liver transplantation; Posttransplantation**

1. Introduction

Transplantation of patients with cirrhosis and hepatorenal syndrome (HRS) represents a major challenge in liver transplantation today due to two main reasons: first, patients with HRS have a very poor short-term prognosis [1,2] which account for a high mortality while awaiting transplantation. Second, the existence of HRS is associated with a poor outcome after transplantation. Several studies from different transplant centers have convincingly demonstrated that renal function pretransplantation is the most important predictive factor of post-transplant survival [3–9]. Moreover, the presence of HRS also carries an increased risk of complications post-transplantation, including intraabdominal bleeding and infections, and a greater use of medical resources (longer hospitalizations and prolonged stays in the intensive care unit) [3,4,6,10,11].

Considering their poor prognosis, patients with HRS are given priority for transplantation in some centers. This was

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* Corresponding author. Tel.: +34-93-227-5499; fax: +34-93-451-5522.
E-mail address: gines@medicina.ub.es (P. Ginès).

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done with the former system of organ allocation used by the United Network for Organ Allocation (UNOS), in which patients with HRS were given the status 2a [12], and is also done by the new system using the model for end-stage liver disease (MELD) score, which includes serum creatinine as one of the variables used to calculate the score [13–17]. This type of priorization without doubt increases the proportion of patients with HRS reaching transplantation but has probably no impact in improving the overall outcome of patients transplanted with HRS. A second issue in patients with HRS is that of the management of renal failure pretransplantation. In many centers, patients are treated with a number of methods of renal support, including hemodyalisis, hemofiltration, or albumin dialysis [18–21]. However, there is no information available about the possible beneficial effect of these measures on outcome after transplantation. Therefore, the management of renal failure pretransplantation in patients with HRS is an unsolved issue.

Recently, several vasoconstrictor drugs have been used in the management of patients with HRS with excellent results [22–28]. The rationale of this treatment is to increase renal perfusion by causing a vasoconstriction of the splanchnic circulation which is extremely vasodilated in patients with HRS [29]. Vasopressin analogues, especially terlipressin, have been used in most studies, but alfa-adrenergic agonists (noradrenaline and midodrine) seem also effective [27,28]. A positive response with reversal of HRS is obtained in up to 75% of patients treated. Furthermore, responder patients have a significantly longer survival compared with non-responders, which suggests that this therapy improves survival [25,26]. Theoretically, the administration of vasoconstrictors may be an ideal approach for the management of HRS in patients awaiting liver transplantation, because the improvement of renal function prior to transplantation may improve posttransplantation outcome. However, the evolution of patients transplanted after treatment of HRS has not been investigated. Therefore, the current study was designed to assess the outcome after transplantation of a series of patients with HRS treated with vasopressin analogues prior to transplantation.

2. Patients and methods

From 1996 to 2001 60 patients with cirrhosis and renal failure admitted to the Liver Unit of the Hospital Clínic of Barcelona met the diagnostic criteria of HRS [30]. Thirty-eight patients (63%) had contraindications for transplantation (advanced age in 16 cases, alcohol abuse in 10, and severe extrahepatic diseases in the remaining 12), while 22 (37%) did not have contraindications. All but one of these 22 patients received vasopressin analogues as therapy for HRS in the setting of prospective studies assessing the efficacy and safety of these drugs in the management of HRS [22,24,26]. Of the 21 transplant candidates with HRS treated (11 with type 1), 16 patients (76%) responded to treatment (reduction of serum creatinine of greater than 25% with respect to pretreatment value with a final value lower than 1.5 mg/dL), while five patients (24%) did not respond. Nine of the 16 responders (56%) were transplanted as compared with only one of the five non-responders (20%; $P = 0.3$) (Table 1). Ten of the 11 patients not transplanted died while awaiting transplantation and one patient was lost to follow-up. Fig. 1 shows the transplant-free survival of the 21 patients with HRS treated divided in two groups according to response to therapy. Median transplant-free survival was 5 months in responders as compared with only 0.4 months in non-responders ($P < 0.001$).

Table 1
Response to treatment and transplantation in the 21 transplant candidates with hepatorenal syndrome (HRS) treated with vasopressin analogues divided according to the type of hepatorenal syndrome

	Transplanted	Non-transplanted
Type 1 HRS ($n = 11$)		
Responders ($n = 6$)	3/6	3/6
Non-responders ($n = 5$)	1/5	4/5
Type 2 HRS ($n = 10$)		
Responders ($n = 10$)	6/10	4/10
Non-responders ($n = 0$)	–	–

2.1. Hepatorenal syndrome group

The current study reports the outcome after transplantation of nine of the ten patients with HRS treated with vasopressin analogues who reached liver transplantation. The remaining patient was not included because he developed an acute glomerulonephritis 12 months after treatment and was subsequently treated with a liver and kidney transplant. Three patients had type 1 HRS and six type 2 HRS [30]. All patients had severe renal failure, as indicated by a very low glomerular filtration rate, as estimated by inulin clearance (15 ± 4 ml/min, range 2–39 ml/min), high serum creatinine concentration (mean 2.7 ± 0.3 mg/dL, range: 1.6–4.7 mg/dl) and blood urea nitrogen (BUN) levels (66 ± 8 mg/dL, range: 30–110 mg/dL), and low urine output (503 ± 75 ml/day, range: 100–800 ml/day). Moreover, all patients had severe circulatory dysfunction, as indicated by low mean arterial pressure (72 ± 5 mmHg, range: 49–93 mmHg) and marked activation of the renin-angiotensin system (plasma renin activity: 14.3 ± 5.3 ng/ml per h, range: 5.2–51 ng/ml per h, normal values: 1.2 ± 0.1 ng/ml per h; aldosterone 229 ± 52 ng/dL, range: 80–470 ng/dL, normal values: 24 ± 2 ng/dL) and sympathetic nervous system (norepinephrine: 1354 ± 420 pg/ml, range: 351–3906 pg/ml, normal values 233 ± 17 pg/ml). All nine patients received vasopressin analogues associated with iv albumin (Albúmina Humana Grifols al 20%; 20 g of

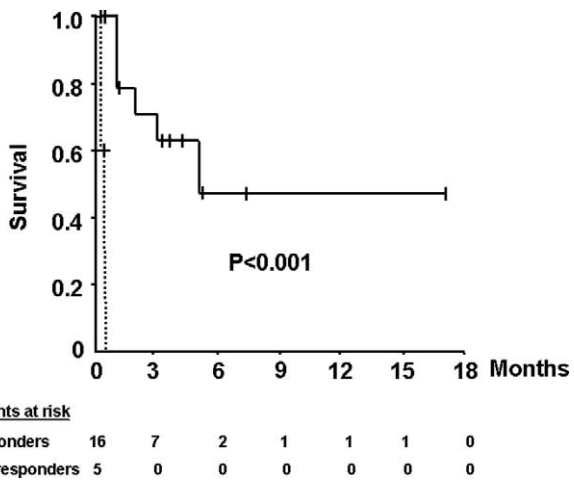

Fig. 1. Probability of transplant-free survival in the 21 patients candidates to transplantation who received treatment with vasopressin analogues for Hepatorenal syndrome divided according to response to therapy: responders (continuous line) and non-responders (discontinuous line). The small vertical lines in each curve represent the time of transplantation of the patients who were transplanted during follow-up.

Albumin/100 ml, Grifols International S.A. Barcelona, Spain) at a dose of 1 g/kg of body weight during the first day and 20–40 g/day thereafter. Six patients received terlipressin (Glypressin; Ferring AB, Malmö, Sweden; mean dose: 5 mg/day, range 3–10 mg/day) and three ornipressin (Por-8 Sandoz, Sandoz Pharma, Basel Switzerland; mean dose 3.7 IU/h, range 3.3–4 IU/h). The schedule used for the administration of each drug is described in the detail elsewhere [22,24]. As described before, eight of the nine patients included (89%) showed a response to treatment after a median of 4 days (range 3–10 days). In one patient, renal function worsened despite the administration of high doses of terlipressin (2 mg/4 h) for up to 9 days. In seven of the eight responders, renal failure did not recur during the period included between treatment withdrawal and transplantation (serum creatinine at the end of treatment: 1.2 ± 0.1 vs 1 ± 0.1 mg/dl at transplantation, $P = 0.28$). In only one patient (11%) HRS recurred 58 days after therapy and was effectively treated with terlipressin. None of the patients received diuretics during follow-up. The recurrence of ascites was treated by large-volume paracentesis plus iv albumin. The median time elapsed between the end of treatment and transplantation was 26 days (range 1–208 days).

2.2. Control group

To evaluate the effects of treatment of HRS before transplantation on clinical course after transplantation, several outcome variables obtained in the HRS group were compared with those from a control group of patients transplanted without HRS. This control group of patients with cirrhosis without renal failure was identified from all patients transplanted during the same period (1996–2001). For each patient with HRS treated, three patients without HRS were identified matched for four variables: age, severity of liver disease, type of immunosuppressive drug used after transplantation, and period of transplantation (1996–1998 and 1999–2001). The first three variables were selected because of their potential effect on renal function and other outcome variables, while the last variable was chosen to cope with possible effects of changes in the general management of patients during the 6 years of the study.

2.3. Surgical technique and postoperative care

Surgical and anesthetical procedures performed both in donors and recipients did not change during the study period [31]. All patients were treated with the surgical technique of preservation of the vena cava (piggyback technique). After transplantation, patients were transferred to the liver ICU and managed postoperatively following a standardized protocol. Initial immunosuppressive therapy consisted of corticosteroids and cyclosporine A or tacrolimus. In patients with low urine volume (urine output lower than 50 ml/h) and/or serum creatinine ≥ 1.5 mg/dL within the first 24 h after transplantation the initiation of cyclosporine A or tacrolimus was delayed until an improvement in these two parameters was observed. In the meantime patients were treated with azathioprine or mycophenolate mofetil. The doses of cyclosporine A or tacrolimus were adjusted according to the blood levels of the drug. The dose of corticosteroids was progressively decreased and discontinued 1–2 years after transplantation.

2.4. Outcome variables

Survival was evaluated at 6 months and 3 years after transplantation. Complications analyzed were: renal failure, intraabdominal bleeding, infections, and acute rejection. Intraabdominal bleeding was assessed during surgery and within the first week posttransplant, while the development of renal failure, severe infections, and acute rejection were evaluated within the first 6 months after transplantation. In addition, the time spent in the ICU and the total duration of the hospitalization were also analyzed.

Renal failure after transplantation was arbitrarily defined as an increase in serum creatinine of greater than 50% of the pretransplant value to a final value greater than 2.5 mg/dL. Severe infection was defined by the presence of systemic or local signs of infection requiring the administration of antibiotics. Acute rejection was defined by the presence of histological features of rejection quantified according to semiquantitative scale (0 = absent, 1 = mild, 2 = marked) during 1996 and 1997 and to Banff criteria afterwards [32].

2.5. Statistical methods

Comparisons between the two groups were performed using the non-parametric Mann–Whitney test for continuous data and the chi-square test and Fischer test for categorical data. The probability of survival and that of development of renal failure were calculated using the Kaplan–Meier method and compared with the Mantel–Cox test. Statistical analyzes of the data were performed by using the SPSS 10 statistical software (SPSS Inc. and Microsoft Corp., Chicago, IL). Results are given as mean ± SE.

Table 2
Baseline characteristics of patients with cirrhosis and hepatorenal syndrome treated (HRS-treated), both immediately before treatment and at transplantation, and of patients with cirrhosis without HRS (no-HRS) at transplantation

	HRS-treated ($n = 9$)		No-HRS ($n = 27$) At transplantation	P[a]
	Before treatment	At transplantation		
Age (years)	50 ± 2	50 ± 2	52 ± 1	0.4
Sex (male/female)	4/5	4/5	18/9	0.4
Etiology of cirrhosis				0.4
Alcoholic	2	2	7	
HCV-positive	4	4	13	
HBV-positive	2	2	1	
Other	1	1	6	
Bilirubin (mg/dL)	13 ± 6	16 ± 7	5 ± 1	0.8
Albumin (g/l)	33 ± 3	35 ± 1	29 ± 1	0.003
Prothrombin time (%)	41 ± 7	46 ± 10	48 ± 4	0.6
Child-Pugh				
Class B/C	2/7	4/5	12/15	1
Score	11 ± 0.7	10 ± 0.7	10 ± 0.3	0.8
Ascites (0/1/2/3)	0/0/3/6	0/1/4/4	3/5/13/6	0.4
Serum creatinine (mg/dL)	2.7 ± 0.4	1.3 ± 0.2	0.9 ± 0.04	0.06
Blood urea nitrogen (mg/dL)	66 ± 8	52 ± 10	20 ± 3	0.001
Serum sodium (mEq/l)	127 ± 2	134 ± 1	132 ± 1	0.4

[a] P between HRS-treated patients and no-HRS patients at the time of transplantation.

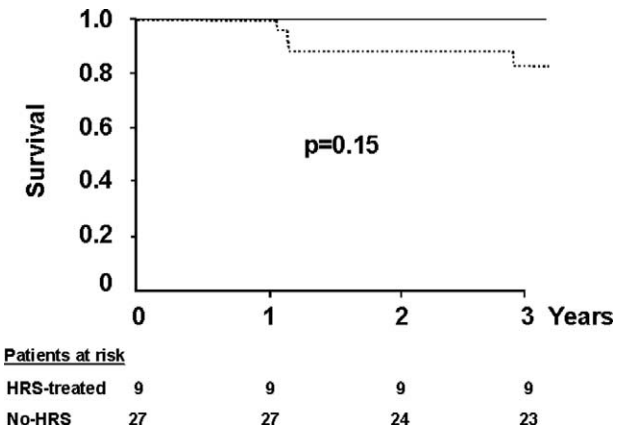

Fig. 2. Three-year probability of survival after transplantation of patients with hepatorenal syndrome treated with vasopressin analogues before transplantation (continuous line) and patients without renal failure (discontinuous line).

3. Results

3.1. Comparison between the two groups

Table 2 shows the demographic, clinical, and biochemical data of patients with HRS, both at the time of treatment and transplantation, and those of the control group of patients without HRS at the time of transplantation. As expected, at transplantation both groups were similar with respect to the matching variables age and severity of liver failure. Moreover, there were no significant differences between the two groups with respect to the other baseline variables except for BUN and serum creatinine, which were higher in the HRS-treated group compared with values in control group. Serum albumin was higher in the HRS-treated group probably due to the administration of albumin during treatment of HRS or in follow-up paracentesis.

3.2. Survival

During follow-up, no patient in the HRS-treated group died, while four of the 27 (15%) patients in the control group died at 13, 14, 14, and 35 months after transplantation. Causes of death were: sepsis in two patients, and pharyngeal cancer and lymphoma in the other two. Survival rate at 6 months was 100% in the two groups. Three-year probability of survival was 100% in the HRS-treated group and 83% in the control group ($P = 0.15$) (Fig. 2).

3.3. Renal function post-transplantation

Fig. 3 shows the mean values of serum creatinine and BUN levels in the two groups of patients during the first 6 months after transplantation. No significant differences were observed in these parameters between the two groups except for a slightly lower BUN values at 1 month in patients in the control group. This lack of differences in renal function parameters occurred despite the existence of a significantly impaired renal function pretransplantation in patients in the HRS-treated group (Table 2). Two patients in the HRS-treated group (22%) and eight patients in the control group (30%) developed renal failure (see definition in Section 2) within the first 6 months after transplantation ($P = 0.7$). The probability of developing renal failure was similar in the two groups (Fig. 4). All episodes of renal failure occurred within the first month after transplantation (median: 3 days), except for one patient of the control group who developed renal failure 5 months after transplantation. Peak creatinine values were 3.9 and 2.7 mg/dL in the two patients from HRS-treated group. In the eight patients from the control group mean peak serum creatinine value was 4 ± 0.7 mg/dL (range 2.7†9 mg/dL). No patient required hemodyalisis. In all patients renal function improved after the correction of the precipitating cause and/or reduction of dosage of immunosuppressive drugs (in the two HRS-treated patients serum creatinine levels decreased to 1 and

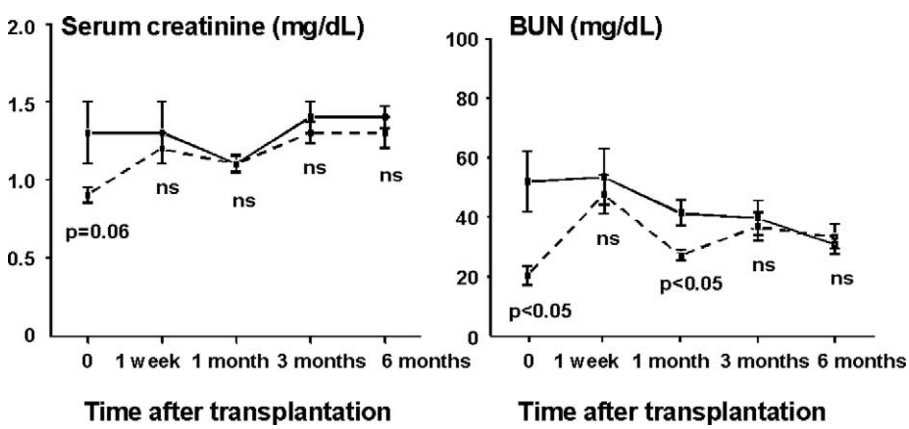

Fig. 3. Mean values of serum creatinine and BUN during the first 6 months after transplantation in patients with hepatorenal syndrome treated with vasopressin analogues before transplantation (continuous line) and patients without renal failure (discontinuous line).

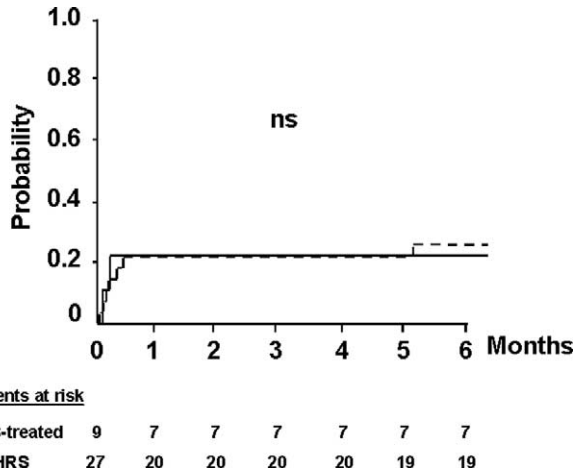

Fig. 4. Probability of developing renal failure during the first 6 months after transplantation in patients with hepatorenal syndrome treated with vasopressin analogues before transplantation (continuous line) and patients without renal failure (discontinuous line).

1.3 mg/dL, while in the eight patients from the control group serum creatinine decreased to 1.2 ± 0.3 mg/dL).

Seven patients from the HRS-treated group and 21 patients from the control group were treated with cyclosporine A, while two and six patients, respectively, received tacrolimus. The mean time elapsed between transplantation and start of cyclosporine A or tacrolimus administration was 1.5 ± 0.5 days in the HRS treated group and 1 ± 0.5 days in the control group ($P = 0.034$). No significant differences were found between the two groups with respect to blood cyclosporine levels at 1 week, 1 month, 3 months, and 6 months. Tacrolimus blood levels were also similar between the two groups.

Table 3
Incidence of severe infection and acute rejection within the first 6 months after transplantation and transfusion requirements in the two groups

	HRS-treated ($n = 9$)	No HRS ($n = 27$)	P
Severe infections			
Patients (n)	2 (22%)	9 (33%)	0.7
Episodes (n)	4	10	
Types of infections			
Respiratory tract	–	7	
Urinary tract	1	–	
Biliary tract	2	–	
Other	1	3	
Acute rejection			
Patients	3 (33%)	11 (41%)	1
Episodes	3	11	
Transfusion requirements[a]			
Intraoperative	7 ± 2	7 ± 1	0.8
First week after transplantation[b]	4 ± 2	3 ± 1	0.3
Total	11 ± 3	10 ± 2	0.7

[a] Units of packed red blood cells.
[b] Excluding transfusion during transplantation.

3.4. Other complications post-transplantation

Two patients in the HRS-treated group developed four episodes of severe infection within the first 6 months after transplantation compared with ten episodes in nine patients in the control group ($P = 0.7$). The types of infection are shown in Table 3. Acute rejection occurred with a similar frequency in patients in the two groups (Table 3). All patients responded to the administration of high-doses of corticosteroids. The intensity of intraabdominal bleeding, as assessed by the number of packed red blood cells transfused both intraoperatively and during the first 7 days after transplantation, was similar in the two groups (Table 3). The duration of the stay in the ICU as well as the total duration of the hospitalization were also similar between the two groups (mean: 6 ± 1 vs 8 ± 1 days and 27 ± 4 vs 31 ± 4 days, respectively, $P =$ ns for both).

4. Discussion

The current study shows that patients with HRS treated with vasopressin analogues and albumin prior to transplantation have an excellent outcome after transplantation, which is not different from that observed in a control group of patients transplanted without HRS matched by age, type of immunosuppression, and severity of the liver disease.

Both short and long-term survival after transplantation of patients with treated HRS were similar to those of a control group of patients transplanted without HRS. The excellent 3-year probability of survival observed in our group of patients with HRS (100%) contrasts sharply with that reported in most studies for patients transplanted with HRS who did not receive treatment for HRS before transplantation, which is approximately of 60% [6–8]. Besides the assessment of survival, and important objective of the current study was to determine the effects of therapy of HRS before transplantation on the evolution of renal function after transplantation. Interestingly, no significant differences were found in serum creatinine and BUN levels at different time points throughout the follow-up between the groups of patients with HRS treated and that of controls. This occurred despite the fact that serum creatinine and BUN levels at the time of transplantation were significantly higher in patients with treated HRS compared with values in patients without HRS and that no special non-nephrotoxic immunosuppressive regime was administered in the group of patients with HRS (Fig. 3). Moreover, the probability of renal failure during follow-up was similar between the two groups. Finally, no patient with treated HRS required hemodyalisis after transplantation.

The frequency of other severe complications after transplantation in patients with treated HRS was similar to that observed in patients transplanted without HRS. Neither the incidence of severe infections nor the severity of bleeding, as assessed by the number of units of blood

transfused, was different between the two groups. The average hospital stay as well the average stay in the ICU was also similar in the two groups. Finally, the frequency of acute rejection during the first 6 months after transplantation was also similar between the two groups of patients.

The good outcome observed in this study of patients with HRS treated before transplantation contrasts sharply with the results of previous studies showing that patients transplanted with HRS had a poor survival compared with patients transplanted without HRS and higher incidence of infections and severe intraabdominal bleeding and longer hospital an ICU stays compared with those of patients transplanted without HRS [3,4,6,10,11]. The discrepancies between the results of the current study and those of previous studies do not seem to be due to differences in patient population as patients included in the studies are similar with respect to severity of renal and liver failure. More likely, the overall good outcome after transplantation of patients with HRS observed in the current study is probably due to the fact that patients were transplanted in conditions of a relatively preserved renal function.

Several aspects of the current study deserve specific discussion: (1) the group of patients with HRS treated with vasopressin analogues and albumin is small. Therefore, these results would require confirmation in larger series of patients. Several reasons account for this low number of patients transplanted with HRS. First, in recent years, the prevalence of HRS among patients with advanced cirrhosis admitted to our institution has decreased markedly compared to previous years. This may be due, at least in part, to the use of effective measures in the prevention of HRS, including early diagnosis and treatment of complications that may trigger the development of HRS, such us infections and gastrointestinal bleeding and administration of albumin to patients with spontaneous bacterial peritonitis [33,34]. In an ongoing prospective study of renal failure in patients with cirrhosis being carried out at our institution, only 11 out of 142 (8%) episodes of renal failure in a 1-year period were due to HRS (Restuccia T, unpublished data). Other factors explaining the low number of patients included is that in our institution patients with HRS were not given priority for transplantation and many other patients with HRS had contraindications to transplantation, mainly active alcoholism and advanced age. Thus, the recruitment of a large series of patients with HRS treated before transplantation would require a multicenter approach; (2) the ideal study design to test the hypothesis of the current investigation would have been that of a prospective randomized study comparing the outcome of patients with HRS treated before transplantation with that of a control group of patients with HRS not treated before transplantation. This was not made because all patients with HRS candidates to transplantation seen at our institution since 1996 were treated with vasopressin analogues and albumin due to the high efficacy of the treatment and the absence of alternative effective therapies. To cope with the lack of a control group of transplanted patients with non-treated HRS, the outcome of the HRS-treated patients was compared with that of a group of patients without HRS transplanted during the same period of time and matched for four important variables: age, severity of liver disease, type of immunosuppression, and period of transplantation; and (3) finally, it is important to remark that the conclusions of our study only apply to the management of HRS and not to renal failure due to parenchymal renal diseases or other causes. Patients with advanced cirrhosis and renal failure due to parenchymal renal diseases (i.e. glomerulonephritis) should probably be treated with liver/kidney transplantation [35].

In conclusion, this study suggests that HRS should be treated before liver transplantation because the improvement in renal function appears to be associated with better overall outcome after transplantation.

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