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Terlipressin Plus Albumin Versus Midodrine and Octreotide Plus Albumin in the Treatment of Hepatorenal Syndrome: A Randomized Trial

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Hepatorenal syndrome (HRS), a serious complication of cirrhosis, is associated with high mortality without treatment. Terlipressin with albumin is effective in the reversal of HRS. Where terlipressin is not available, as in the United States, midodrine and octreotide with albumin are used as an alternative treatment of HRS. The aim was to compare the effectiveness of terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of HRS in a randomized controlled trial. Twenty-seven patients were randomized to receive terlipressin with albumin (TERLI group) and 22 to receive midodrine and octreotide plus albumin (MID/OCT group). The TERLI group received terlipressin by intravenous infusion, initially 3 mg/24 hours, progressively increased to 12 mg/24 hours if there was no response. The MID/OCT group received midodrine orally at an initial dose of 7.5 mg thrice daily, with the dose increased to a maximum of 12.5 mg thrice daily, together with octreotide subcutaneously: initial dose 100 μg thrice daily and up to 200 μg thrice daily. Both groups received albumin intravenously 1 g/kg of body weight on day 1 and 20-40 g/day thereafter. There was a significantly higher rate of recovery of renal function in the TERLI group (19/27, 70.4%) compared to the MID/OCT group (6/21, 28.6%), P = 0.01. Improvement in renal function and lower baseline Model for End-Stage Liver Disease score were associated with better survival. *Conclusion:* Terlipressin plus albumin is significantly more effective than midodrine and octreotide plus albumin in improving renal function in patients with HRS (HEPATOLOGY 2015;62:567-574)

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Hepatorenal syndrome (HRS) is a potentially reversible form of renal failure that occurs in patients with cirrhosis and ascites.[1-4] According to the peripheral arterial vasodilatation hypothesis,[5] HRS is caused by severe renal arterial vasoconstriction in response to reduction in the effective circulating volume. Renal vasoconstriction is mediated by the renin-angiotensin and sympathetic nervous systems and the nonosmotic release of vasopressin. The reduction in the effective circulating volume is a consequence of marked splanchnic arterial vasodilatation and low cardiac output. Bacterial infections precipitate HRS by increasing vasodilatation and worsening the cardiocirculatory dysfunction of cirrhosis. There are two types of HRS. Type 1 HRS is characterized by rapid progressive renal failure defined by doubling of the initial serum creatinine concentrations to a level

Abbreviations: HRS, hepatorenal syndrome; MAP, mean arterial pressure; MELD, Model for End-stage Liver Disease.

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greater than 226 μmol/L (2.5 mg/dL) in less than 2 weeks. Type 2 HRS is characterized by moderate renal failure (serum creatinine 133-226 μmol/L or 1.5-2.5 mg/dL), with a steady or slowly progressive course.[4]

Median survival in untreated patients with HRS may be as short as 2 weeks; liver transplantation is the treatment of choice.[6] However, patients with HRS have a high mortality rate while awaiting transplant. Moreover, post–liver transplant survival rates in patients with HRS are lower than in patients without HRS.[7]

Use of a splanchnic arterial vasoconstrictor is associated with improvement in renal function in type 1 HRS.[8-13] Terlipressin, a vasopressin derivative, is the most widely used vasoconstrictor in Europe because of its effectiveness and ease of administration[4]; and it improves renal function in 40%-50% of patients.[14-19] In countries such as the United States, where terlipressin is not available, midodrine and octreotide with albumin[8] have been used in uncontrolled studies to treat HRS, with reported reversal of HRS as high as 40%.[20-22] Midodrine is an alpha1-adrenergic agonist which causes splanchnic vasoconstriction. Octreotide, a somatostatin analogue, enhances the splanchnic vasoconstriction by inhibiting glucagon-mediated splanchnic vasodilatation. However, the combination of midodrine and octreotide has not been compared with terlipressin in the treatment of HRS. Therefore, the aim of this study was to compare terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of HRS in patients with cirrhosis.

Patients and Methods

Inclusion and Exclusion Criteria. After institutional review board approval at each institution and trial registration (NCT00742339), patients were entered into the study following written informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Inclusion criteria included cirrhosis diagnosed by liver biopsy or clinical, biochemical, ultrasound, and/or endoscopic findings; type 1 or severe type 2 HRS as defined by International Ascites Club criteria of serum creatinine level >226 μmol/L (2.5 mg/dL)[2,4]; and age 18-75 years. Exclusion criteria were hepatocellular carcinoma outside Milan criteria,[23] septic shock, cardiac or respiratory failure, stroke, or coronary artery disease.

Definitions of Response to Treatment. *Complete response* was defined as a decrease in serum creatinine to ≤133 μmol/L (≤1.5 mg/dL). *Partial response* was defined as a ≥50% serum creatinine decrease from baseline to a final value >133 μmol/L (>1.5 mg/dL). *No response* was defined as a serum creatinine decrease of <50% from baseline.

Study Design. Diuretic agents were withheld, and albumin (1 g/kg body weight) was infused intravenously for 48 hours for plasma expansion in all eligible patients.[2,4] Patients who then met inclusion criteria were entered into the study and randomized to receive terlipressin plus albumin or midodrine and octreotide plus albumin.

Patients were randomized at each hospital using sealed opaque envelopes containing the treatment assignments based on random numbers generated by the Stata statistical package (version 7.0, 1999; Stata Corp, College Station, TX). Patients with type 1 HRS were randomized independently from those with type 2 HRS.

Demographic, clinical, and laboratory data; vital signs; and Model for End-stage Liver Disease (MELD) scores were recorded at the time of inclusion. Physical examination, electrocardiogram, chest X-ray, and routine laboratory tests were performed in all patients at regular intervals during treatment.

In all patients included in the study, albumin (Albumina 20%; Kedrion S.p.A., Barga, Italy) was administered intravenously, 1 g/kg at day 1 and 20-40 g/day subsequently for the duration of the study.

In the TERLI group, terlipressin (Glypressin; Ferring AB, Malmö, Sweden) was administered initially at a dose of 3 mg/24 hours by continuous intravenous infusion. Response to treatment was evaluated every 48 hours. If serum creatinine decreased by <25% of the pretreatment value, the dose of terlipressin was progressively increased to 12 mg/24 hours. In patients randomized to the MID/OCT group, midodrine (Gutron; Lusofarmaco, Peschiera Borromeo, Italy) was

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administered orally at a starting dose of 7.5 mg every 8 hours along with octreotide (Longastatina; Italfarmaco S.p.A., Milan, Italy) administered subcutaneously at a starting dose of 100 μg every 8 hours. If serum creatinine decreased by <25% of the pretreatment value, the dose of midodrine was progressively increased to a maximum of 12.5 mg every 8 hours and octreotide to 200 μg every 8 hours. Terlipressin as well as midodrine plus octreotide were administered until serum creatinine decreased to $\leq$133 μmol/L (1.5 mg/dL) or for a maximum of 14 days. Treatment was maintained for 24 hours after a complete or incomplete response. Treatment was withheld if adverse effects developed such as angina and/or arrhythmia, peripheral ischemia, or severe abdominal pain.

Treating physicians were allowed to start any rescue treatment in nonresponders. After discharge, patients were followed for up to 3 months, liver transplantation, or death. For survival analysis patients were censored at the time of transplant.

Statistical Analysis. The primary endpoint of the study was complete response at completion of treatment, and this was used for sample size calculation. Because terlipressin is a stronger splanchnic arterial vasoconstrictor than midodrine, it was hypothesized that complete recovery of renal function could occur in 60% of patients treated with terlipressin and in 30% of those treated with midodrine plus octreotide. Using a two-tailed test, 43 patients were required in each group, for a P value <0.05 with an α error of 5% and a β error of 20%. An interim analysis was provided after the enrollment of half of the sample size, and a stopping rule for the randomized clinical trial was fixed if the difference in recovery of renal function was significant at $P < 0.01$. The interim analysis was performed by an independent statistician. Results are presented as mean $\pm$ standard deviation for continuous data and proportions for categorical ones. Group or subgroup comparisons were performed using the Student t test or Wilcoxon rank sum tests for continuous data and the chi-squared test or Fisher's exact test for categorical data. Survival was estimated using the Kaplan-Meier method and compared with the log-rank test. Variables that were found to be predictors of response and of survival, with $P < 0.1$ in the univariate analysis, were included in a multivariate logistic regression model; and the results were presented as odds ratios with a 95% confidence interval. All tests were two-tailed. $P < 0.05$ was considered to be statistically significant. Statistical analyses of the data were performed using SPSS 10 statistical software (SPSS Inc. and Microsoft Corp., Chicago, IL).

Results

Patients. The study was terminated after 49 patients were included according to the *a priori* determined stopping rule. A total of 66 patients with cirrhosis and HRS diagnosed between 2008 and 2012 in eight hospitals in Italy were evaluated for inclusion in the study. Seventeen of the 66 patients screened were excluded for reasons outlined in Fig. 1 (consort diagram). The remaining 49 patients were randomly assigned to one of the two treatment groups: 27 to terlipressin plus albumin (TERLI group) and 22 to midodrine and octreotide plus albumin (MID/OCT group). One patient randomized in the MID/OCT group was excluded from analysis of data because of liver transplantation at day 2. A flowchart of patients entered into the study and included in the analysis of data is provided in Fig. 1.

There were no significant differences between the two groups in clinical and laboratory data at the time of enrollment (Table 1). No patient had alcoholic hepatitis. The two groups were also similar with respect to the percentage of patients with type 1 HRS (93% in the TERLI group versus 90% in the MID/OCT group).

Reversal of Renal Failure. Improvement of renal function was significantly more frequent in patients randomized to the TERLI group than in patients randomized to the MID/OCT group (Fig. 2): 19 of 27 patients in the TERLI group (70.4%) had a complete or partial response compared with six of 21 (28.6%) in the MID/OCT group ($P = 0.01$); 15 of 27 patients in the TERLI group (55.5%) had a complete response compared with one of 21 in the MID/OCT group (4.8%) ($P < 0.001$). The reduction of serum creatinine in all responders was higher in the TERLI group (from 323.2 $\pm$ 91.1 to 121.6 $\pm$ 30.0 μmol/L, 3.6 $\pm$ 1.0 to 1.3 $\pm$ 0.3 mg/dL) than in the MID/OCT group (from 332.8 $\pm$ 85.1 to 159.8 $\pm$ 15.9 μmol/L, 3.7 $\pm$ 0.9 to 1.8 $\pm$ 0.2 mg/dL), but the difference was not statistically significant. The reduction of serum creatinine in all patients in the TERLI group (from 326.8 $\pm$ 88.4 μmol/L to 221.1 $\pm$ 162.8 μmol/L) was statistically higher than in the MID/OCT group (from 343.9 $\pm$ 187.5 to 326.4 $\pm$ 273.2 μmol/L; $P = 0.035$). In the TERLI group 13 of the 15 complete responders to treatment responded to 3 mg/day and two responded to 6 mg/day. As far as the four partial

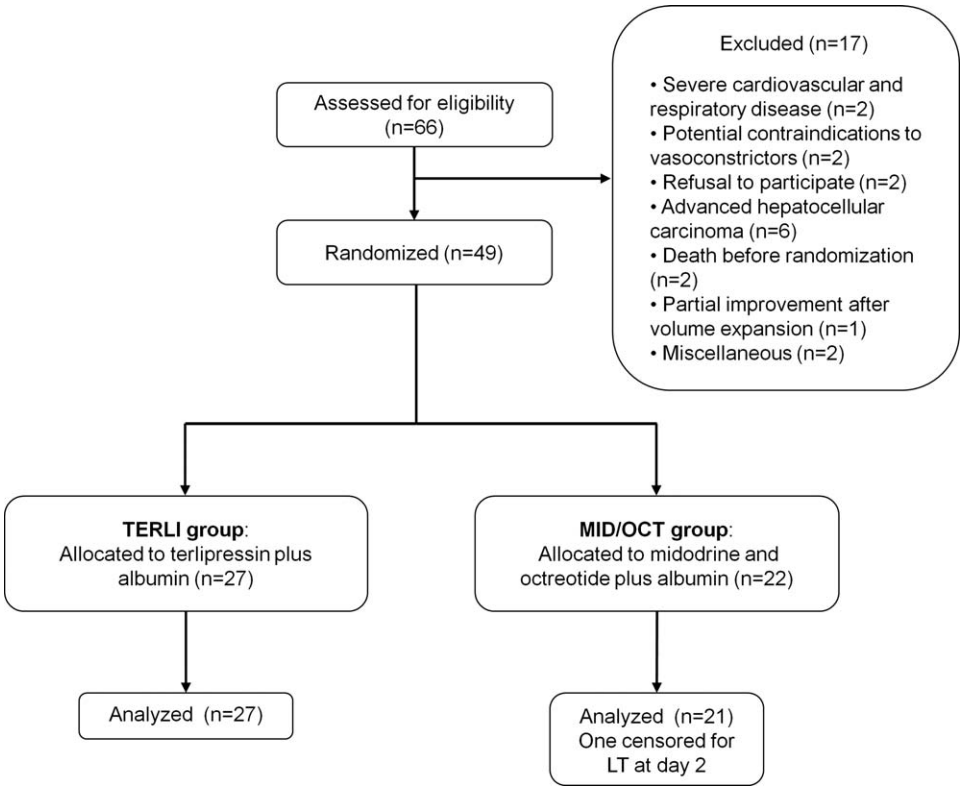

Fig. 1. Study flowchart. Abbreviation: LT, liver transplantation.

Table 1. Demographic, Clinical, and Laboratory Features at Baseline in Patients Who Were Randomized to Terlipressin Plus Albumin (TERLI Group) or to Midodrine and Octreotide Plus Albumin (MID/OCT Group)

Parameter	TERLI Group (n = 27)	MID/OCT Group (n = 21)	P
Age, years	60 ± 12	65 ± 10	NS
Male/female, n	21/6	11/10	NS
Etiology (viral/no viral), n	10/17	8/13	NS
HRS type 1/type 2	25/2	19/2	NS
HRS precipitated by bacterial infections, Y/N	16/11	11/10	NS
MAP, mm Hg	76.8 ± 10.0	75.2 ± 8.1	NS
Heart rate, bpm	77.8 ± 11.5	81.1 ± 13.4	NS
International normalized ratio	2.0 ± 0.5	1.7 ± 0.5	NS
Serum bilirubin, μmol/L	201.1 ± 268.3	187.8 ± 252.4	NS
Serum bilirubin, mg/dl	11.7 ± 15.6	10.9 ± 14.6	NS
Serum creatinine, μmol/L	326.8 ± 88.4	343.9 ± 187.5	NS
Serum creatinine, mg/dL	3.6 ± 1.0	3.8 ± 2.1	NS
Serum sodium, mmol/L	130.8 ± 5.5	133.5 ± 7.7	NS
MELD	31.2 ± 5.8	29.1 ± 8.1	NS
MELD-Na	32.7 ± 4.4	29.8 ± 6.9	NS
Hemoglobin, g/dL	9.9 ± 1.4	9.9 ± 1.5	NS
Serum albumin, g/dL	30.8 ± 3.6	31.8 ± 7.0	NS
Serum urea, mmol/L	23.4 ± 9.4	22.2 ± 11.1	NS
Serum potassium, mmol/L	4.4 ± 1.0	4.6 ± 0.8	NS
Aspartate aminotransferase, U/L	89.0 ± 73.8	68.6 ± 54.6	NS
Alanine aminotransferase, U/L	43.7 ± 24.6	34.9 ± 31.5	NS
Gamma-glutamyl transferase, U/L	69.6 ± 70.9	81.7 ± 80.6	NS

Abbreviation: MELD-Na, Model for End-Stage Liver Disease and Serum Sodium Concentration; NS, nonsignificant.

responders are concerned, all received the maximal tolerated dose, which was 3 mg/day in one patient, 6 mg/day in one patient, and 12 mg/day in the remaining two patients.

The only complete responder in the MID/OCT group responded to 22.5 mg/day of midodrine plus 300 μg/day of octreotide. The five partial responders in the MID/OCT group received the maximal

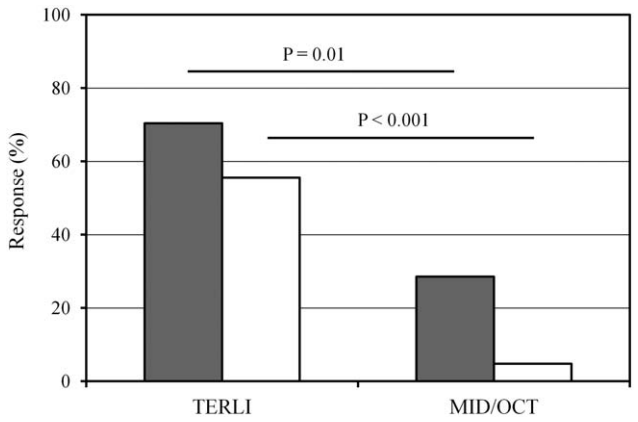

Fig. 2. Rates of response in patients who were randomized to terlipressin plus albumin (TERLI) or to midodrine and octreotide plus albumin (MID/OCT). Gray bars represent patients with complete or partial response; white bars represent patients with complete response.

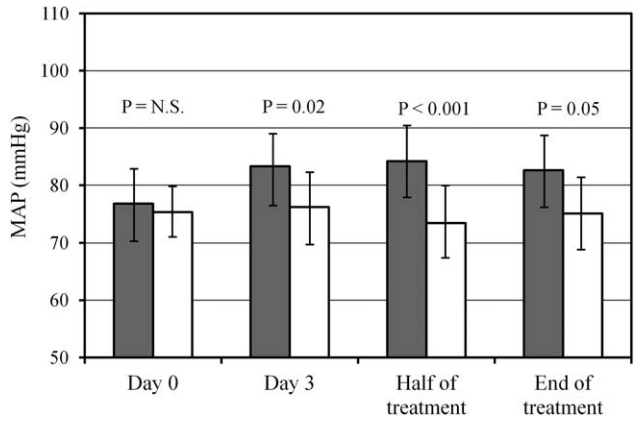

Fig. 3. Mean arterial pressure (MAP) in patients who were randomized to terlipressin plus albumin (TERLI group) or to midodrine and octreotide plus albumin (MID/OCT group) during treatment. Gray bars represent MAP in the TERLI group; white bars represent MAP in the MID/OCT group.

tolerated dose, which was 37.5 mg/day of midodrine plus 600 μg/day of octreotide in four patients and 22.5 mg/day of midodrine plus 300 μg/day of octreotide in the remaining one patient.

There were no significant differences between the two groups of patients with respect to the duration of treatment (8.2 ± 4.4 days in the TERLI group versus 9.1 ± 5.0 days in the MID/OCT group; P = nonsignificant) or the cumulative albumin dose after the initial load (264.8 ± 200.2 g versus 313.6 ± 185.4 g; P = nonsignificant).

Mean arterial pressure (MAP) was significantly higher in the TERLI group versus the MID/OCT group after 3 days of treatment as well as at the midpoint of the treatment period (Fig. 3).

Predictors of Reversal of HRS. In univariate analysis the presence of bacterial infection as a precipitating event of HRS, baseline MELD score, serum creatinine, serum bilirubin, MAP, and delta MAP at the third day of treatment were not found to be predictors of response to treatment (Table 2). In multivariate analysis only delta MAP at the third day and randomization (TERLI group versus MID/OCT group) were included. The only independent predictor of reversal of HRS was found to be randomization to the TERLI group (hazard ratio = 6.3, 95% confidence interval 1.6-24.4, $P = 0.007$).

Table 2. Clinical and Laboratory Features of Baseline Variables According to Response to Treatment

Parameter	Total Responders (n = 25)	Nonresponders (n = 23)	P
Age, years	62 ± 12	63 ± 12	0.690
HRS precipitated by bacterial infections, Y/N	16/9	11/12	0.383
MAP, mm Hg	77.5 ± 9.8	74.5 ± 8.2	0.267
Delta MAP at 3 days, mm Hg	6.2 ± 8.7	1.5 ± 13.1	0.097
Heart rate, bpm	78.4 ± 11.2	80.6 ± 13.9	0.576
International normalized ratio	2.0 ± 0.6	1.8 ± 0.4	0.183
Serum bilirubin, μmol/L (mg/dL)	166.8 ± 212.2 (9.7 ± 12.3)	229.9 ± 307.7 (13.3 ± 17.8)	0.433
Serum creatinine, μmol/L (mg/dL)	325.5 ± 88.0 (3.6 ± 1.0)	343.8 ± 180.5 (3.8 ± 2.0)	0.669
MELD	31.0 ± 6.4	29.5 ± 7.4	0.450
Serum albumin, g/dL	30.4 ± 3.5	32.4 ± 7.0	0.372
Randomization, TERLI group versus MID/OCT group	19/6	8/15	0.008

Rescue Treatment. Some nonresponders to the assigned treatment received a rescue treatment (if they were still alive) according to the treating physician's decision. Five nonresponders in the TERLI group and three nonresponders in the MID/OCT group died before any rescue treatment. One patient out of three (33.3%) nonresponders in the TERLI group received a rescue treatment with dialysis. Seven of 12 (58.3%) nonresponders in the MID/OCT group received a rescue treatment: six received terlipressin plus albumin, and one received dialysis. An improvement of renal function was observed in five of six patients (83.3%) who received terlipressin plus albumin, which was complete in four patients and partial in one.

Survival. There were no significant differences between the two groups with respect to number of patients who were alive at 1 and 3 months: 19/27 (70%) and 16/27 (59%), respectively, in the TERLI group, and 14/21 (67%) and 9/21 (43%), respectively, in the MID/OCT group (P = nonsignificant). Responders to assigned treatment showed a better survival than nonresponders ($P < 0.001$). Figure 4 shows the cumulative survival of patients included in the study at 3 months classified according to response to randomized treatment, terlipressin plus albumin (left graph) and midodrine and octreotide plus albumin (right graph). The difference in cumulative survival between all responders (partial and full responders) and nonresponders was statistically significant in the TERLI group ($P < 0.001$) but not in the MID/OCT group (P = nonsignificant). Regarding the potential role of rescue treatment in this discrepancy, a higher 3-month survival rate in patients who did not receive any rescue treatment in the TERLI group than in the MID/OCT group was found (55.5% versus 28.6%, $P = 0.06$). Finally, considering all the randomized patients as a whole, a significant difference in cumulative survival at 3 months was observed when patients with a reduction in serum creatinine $\geq$50% from baseline were compared to patients with a reduction in serum creatinine $<$50% from baseline (73.7% versus 37.9%, respectively; $P < 0.025$).

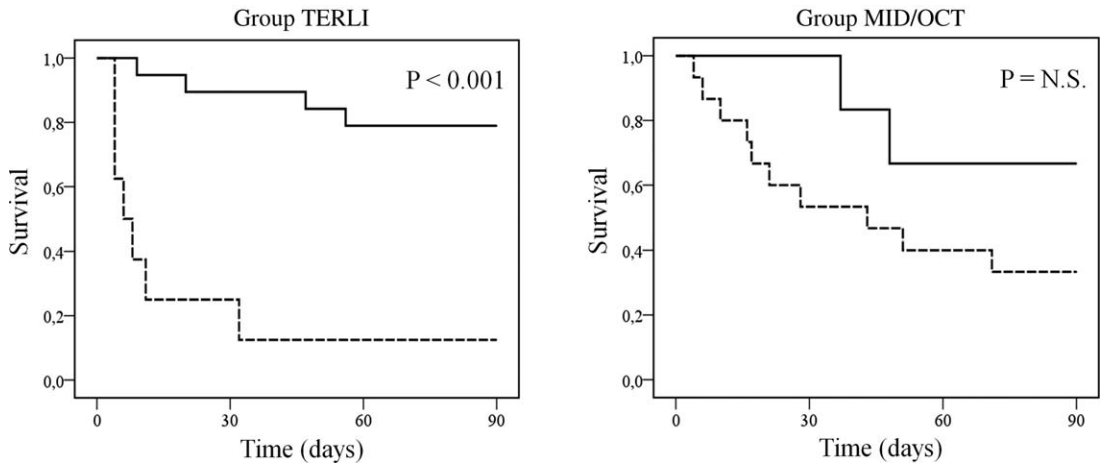

Fig. 4. Cumulative 3-month survival in patients who were randomized to terlipressin plus albumin (TERLI group) or to midodrine and octreotide plus albumin (MID/OCT group) according to the response: solid line represents responders; dotted line represents nonresponders. Abbreviation: N.S., nonsignificant.

Predictors of Survival. Among all patients entered into the study, only response (complete or partial) to treatment was found to be a predictor of 3-month survival in the univariate analysis (Table 3a). In multivariate analysis, response to treatment and baseline MELD score were predictors of 3-month survival (Table 3b).

Adverse Events. We found no significant differences in adverse events supposed to be associated with assigned treatment (Table 4). Adverse events led to discontinuation of treatment in one patient in the TERLI group (stroke) and one patient in the MID/OCT group (grade 4 bradycardia). The former died as a consequence of stroke.

Discussion

On the basis of the large benefit in renal response to terlipressin plus albumin compared with midodrine and octreotide plus albumin, the study was terminated after the interim analysis, according to the provided stopping rule.

Improvement in renal function was associated with a significant increase in arterial pressure in both groups, confirming the existence of a major relationship between circulatory and renal function in patients with HRS.[24-26] The greater effect of terlipressin treatment on increasing MAP may explain the higher efficacy of terlipressin plus albumin over midodrine and octreotide plus albumin in improving renal function (Fig. 3). Of importance, there were no differences in adverse events between the groups.

The rate of renal response to midodrine (28.6%) may be considered in the range of the results obtained in clinical practice. Nevertheless, it was lower than the response observed in a previous larger retrospective study (40%).[22] In order to explain this discrepancy, it should be highlighted that in the retrospective study by Esrailian et al.[22] (1) the plasma volume expansion for the diagnosis of type 1 HRS was performed also with

Table 3a. Univariate Analysis of Predictors for 3-Month Survival

Parameter	Hazard Ratio	95% Confidence Interval	P
Randomized treatment	0.52	0.16-1.64	0.26
Response to treatment	8.97	2.43-33.16	0.001
Baseline MELD	1.09	0.99-1.20	0.07

Table 3b. Multivariate Analysis of Predictors for 3-Month Survival

Parameter	Hazard Ratio	95% Confidence Interval	P
Response to treatment	22.93	3.17-165.86	0.002
Baseline MELD	1.19	1.03-1.37	0.02

Table 4. Adverse Events Supposed to Be Related to the Randomized Treatment

	TERLI group (n = 27)	MID/OCT group (n = 21)	P
Abdominal pain	2 (7.4%)	3 (14.3%)	NS
Diarrhea	2 (7.4%)	0	NS
Arrhythmia	0	2 (9.5%)	NS
Circulatory overload	1 (3.7%)	1 (4.8%)	NS
Arterial hypertension	1 (3.7%)	0	NS
Stroke	1 (3.7%)	0	NS
Total	7 (25.9%)	6 (28.6%)	NS

Adverse events led to discontinuation of assigned treatment in one patient in the TERLI group and one patient in the MID/OCT group.

Abbreviation: NS, nonsignificant.

saline alone; (2) more than 50% of treated patients had alcoholic hepatitis, in whom recovery of renal function could have occurred only as a result of the improvement of their liver disease; (3) several patients with alcoholic hepatitis were cotreated with pentoxyphylline; and (4) the treatment with midodrine plus octreotide was not found to be an independent predictor of renal response. One may argue that the rate of complete response in patients of the MID/OCT group was even lower that that observed with albumin alone in the study of Sanyal et al.[17] With that in mind, in the present study the rate of renal response was globally higher than that observed in the study of Sanyal et al. (28.6% versus 18%); again, it should be highlighted that in the study of Sanyal et al. the plasma volume expansion for the diagnosis of type 1 HRS was performed also with saline alone and that 36% of included patients had alcoholic hepatitis. On the other hand, the percentage of patients with partial or complete renal response in the group treated with terlipressin plus albumin appears significantly higher than that found in two main previous controlled trials in terms of either complete response (56% versus 33.9%-39%)[15,17] or complete and partial responses (70% versus 43.5%).[15] We believe that two factors may explain this difference in the rate of response to terlipressin plus albumin. First, in the two previous studies terlipressin was given by intravenous bolus every 4 or 6 hours. This schedule may have reduced the vasoconstrictor effect of terlipressin. In fact, in a pharmacodynamic study performed in patients with cirrhosis, the effect of terlipressin on portal pressure was shown to last less than 4 hours.[27] Therefore, terlipressin was administered as a continuous intravenous infusion in the current study. Second, according to the diagnostic criteria of the International Club of Ascites reported in 2007, patients with renal failure and active bacterial infections are considered as having HRS.[4] Recent observations suggest that the rate of response to terlipressin and albumin in patients with infection related HRS is as high as 67%.[28]

For ethical reasons, a rescue treatment was provided in nonresponders to randomized treatment, including the possibility of crossing over from one study drug regimen to the other. Thus, it is necessary to point out that the study design was not ideal for evaluating the effect of the randomized treatment on the secondary endpoint, which was survival at 1 and 3 months. The "intention to treat" survival at 1 and 3 months was not significantly different in the two groups.

Nevertheless, the results of the study allowed us to make some observations on survival. First, the response to treatment was found to be an independent predictor of survival. Second, the difference in 1-month and 3-month survival between responders and nonresponders was greater in the TERLI group (Fig. 4, left panel) than in the MID/OCT group (Fig. 4, right panel). A great impact of rescue treatment on renal function and/or survival in nonresponders in the MID/OCT group should be considered in order to explain this difference. Thus, 3-month survival was higher in the TERLI group than in the MID/OCT group when only patients who did not receive any rescue treatment were considered. As far as adverse events are concerned, despite the greater vasoconstrictor effect of terlipressin, serious adverse events and/or adverse events that led to treatment discontinuation were not significantly different in the two groups. Nevertheless, stroke and arterial hypertension were observed only in patients who were treated with terlipressin. Circulatory overload and arrhythmia could be related also to factors other than the vasoconstrictor effect, such as renal failure *per se* and/or electrolyte imbalance.

In conclusion, the results of this randomized, comparative study indicate that administration of terlipressin plus albumin is more effective in improving both renal function and survival in patients with cirrhosis and HRS compared with midodrine and octreotide plus albumin. Thus, terlipressin plus albumin should currently be considered the first choice for management of patients with cirrhosis and HRS.

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