

# Hemodynamic Effects of Terlipressin and High Somatostatin Dose during Acute Variceal Bleeding in Nonresponders to the Usual Somatostatin Dose

Càndid Villanueva, M.D., Montserrat Planella, M.D., Carles Aracil, M.D., Josep M. López-Balaguer, M.D., Begoña González, M.D., Josep Miñana, M.D., and Joaquim Balanzó, M.D.  
*Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

- OBJECTIVES:** High dose of somatostatin infusion achieves a greater reduction of hepatic venous pressure gradient (HVPG) than the usual dose, and terlipressin decreases HVPG through mechanisms other than somatostatin. Our aim was to assess the hemodynamic effects of terlipressin and high somatostatin dose during acute variceal bleeding in nonresponders to the usual somatostatin dose.
- METHODS:** Hemodynamic studies were performed in 80 patients with cirrhosis and variceal bleeding during the first 3 days of admission. After baseline measurements, somatostatin was administered (250  $\mu\text{g}/\text{h}$  with an initial bolus of 250  $\mu\text{g}$ ). Patients were considered responders when the HVPG decreased by  $>10\%$  from baseline ( $n = 31$ ). Nonresponders were randomized under double-blind conditions to a control group ( $n = 7$ ), or to receive terlipressin (2 mg IV bolus,  $n = 22$ ), or high dose of somatostatin (500  $\mu\text{g}/\text{h}$ ,  $n = 20$ ). Final measurements were obtained 30 min later.
- RESULTS:** Terlipressin caused a decrease in HVPG (from  $22.2 \pm 5$  to  $19.1 \pm 5.2$ ,  $p < 0.01$ ) and heart rate ( $p < 0.01$ ), while mean arterial pressure increased ( $p < 0.01$ ). High somatostatin dose also reduced HVPG (from  $21.8 \pm 3.4$  to  $19.6 \pm 3.1$ ,  $p < 0.01$ ), although this decrease was more pronounced with terlipressin ( $15\% \pm 9\%$  vs  $10\% \pm 6\%$  from baseline,  $p = 0.05$ ). Both terlipressin and high somatostatin dose achieved a significantly higher rate of response than that in the control group. A decrease in HVPG  $>20\%$  was observed in 36% of cases with terlipressin versus 5% with high somatostatin dose ( $p = 0.02$ ).
- CONCLUSIONS:** In nonresponders to usual somatostatin dose, both terlipressin and high-dose of somatostatin infusion significantly decreased HVPG and increased the rate of hemodynamic responders. Such effects were greater with terlipressin. Both treatments may be an alternative when standard somatostatin fails.

(Am J Gastroenterol 2005;100:624–630)

## INTRODUCTION

Somatostatin is widely used in the treatment of variceal bleeding for its capacity to decrease portal pressure without significant side effects. However, although it is effective to control acute bleeding (1), the rate of failures is not negligible when this treatment is used alone (2). Furthermore, the effects of somatostatin on portal pressure in cirrhotic patients are controversial (3–6). Portal pressure or its equivalent, the hepatic venous pressure gradient (HVPG), is a major determinant of variceal bleeding risk and provides important prognostic information on the course of the acute variceal bleeding episode (7, 8). Bolus injection of somatostatin produces a marked fall in HVPG, which lasts only a few minutes, while the continuous infusion maintains a mild decrease (9). This

moderate effect of somatostatin infusion is not uniform (10), and only in half the cases the HVPG decreases more than 10% from baseline (11). Recent studies have shown that high doses of somatostatin infusion of 500  $\mu\text{g}/\text{h}$  may achieve a more consistent hemodynamic effect than the usual dose of 250  $\mu\text{g}/\text{h}$ , enhancing the decrease of HVPG (9). The effects of somatostatin on splanchnic circulation have been attributed to a vasoconstrictor response mediated by the prevention of the release of vasoactive peptides (12). A direct vasoconstrictive effect achieved by the potentiation of protein kinase C-dependent vasoconstrictors has also been suggested (13, 14).

Terlipressin has an intrinsic vasoconstrictor activity that leads to a decrease in portal venous inflow and to a significant and marked reduction of portal and variceal pressure (15–19). It is also widely used to treat variceal bleeding, and is the only drug shown to improve survival from variceal bleeding in the placebo-controlled trials (1). Because of its

Grant support: This study has been supported in part by a grant from the Fundació Investigació Sant Pau and by a grant from the Instituto de Salud Carlos III (CO3/02).

different mechanisms of action, it may be speculated that terlipressin may be effective when somatostatin does not achieve a decrease in HVPG.

The present study was performed to assess the hemodynamic effects of both terlipressin and high doses of somatostatin infusion (of 500  $\mu\text{g}/\text{h}$ ), in nonresponders to the usual somatostatin dose. Patients were investigated during the acute variceal bleeding episode when the effect of vasopressin and somatostatin on portal pressure may be attenuated (20–22). According to the previous studies, hemodynamic response was defined as a decrease in HVPG below 20 mmHg or  $>10\%$  from baseline, as the risk of failure to control acute variceal bleeding is significantly higher when these targets are not achieved (11, 23). In the current study only nonresponders to standard somatostatin were randomized, thus selecting a high-risk subset of subjects in whom effective treatments are particularly desirable.

## PATIENTS AND METHODS

Cirrhotic patients with acute esophageal variceal bleeding initially controlled with the medical treatment, including somatostatin and emergency sclerotherapy or variceal ligation, and in whom a hemodynamic evaluation could be performed within the first 3 days of admission, were considered for inclusion in this study. All patients were admitted to our hospital with hematemesis and/or melena. Variceal hemorrhage was diagnosed by emergency endoscopy, which was performed within the first 5 h of admission. Cirrhosis was diagnosed by previous liver biopsy or by clinical, biochemical, and echographic findings. Patients were excluded if they fulfilled any of the following criteria: treatment with  $\beta$ -blockers or other vasoactive drugs within the previous 5 days, a Child-Pugh score  $>12$  points, hepatocellular carcinoma, portal vein thrombosis, extrahepatic malignancies, or other severe associated conditions.

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of our hospital. Informed consent was obtained from each patient included in the study.

### Catheterization

Catheterization was performed within the first 3 days of admission. In patients receiving somatostatin, the administration was stopped at least 6 h before hemodynamic measurements. Under local anesthesia, a venous catheter introducer was placed in the right internal jugular or the right femoral vein. It was used to advance, under fluoroscopic control, a Swan-Ganz catheter into the pulmonary artery to measure cardiac output and cardiopulmonary pressures, and a 7F balloon-tipped catheter into the main right hepatic vein to measure wedged (occluded) and free hepatic venous pressures (WHVP and FHVP). All intravascular pressure measurements were performed in triplicate in each period of the study, using a previously calibrated highly sensitive trans-

ducer (Hewlett-Packard 1280 C). Portal pressure was estimated from the HVPG, the difference between WHVP and FHVP. The occluded position of the catheter was checked by the absence of reflux after injection of 2 mL of contrast medium. Electrocardiography, mean arterial pressure (MAP), and heart rate (HR) were monitored throughout the study with an automatic vital signs monitor (Hewlett-Packard M1008A).

### Study Protocol

Once baseline measurements were completed, all patients received a bolus injection of 250  $\mu\text{g}$  of somatostatin followed by the standard dose of 250  $\mu\text{g}/\text{h}$  continuous IV infusion. Ten minutes later, HVPG was measured again and patients were considered responders when the HVPG decreased below 20 mmHg (if it was higher), or by more than 10% from the baseline value. Ten minutes later, nonresponders were randomly assigned into three groups: a control group, a high somatostatin dose group, and a terlipressin group. Patients in the control group received a continuous IV infusion of 250  $\mu\text{g}/\text{h}$  of somatostatin and an injection of placebo (saline). Patients in the high somatostatin dose group received a continuous IV infusion of 500  $\mu\text{g}/\text{h}$  of somatostatin and an injection of placebo. Patients in the terlipressin group received a single IV injection of 2 mg of terlipressin and a continuous IV infusion of placebo. Final hemodynamic measurements were obtained 30 min after the start of continuous IV infusion. Randomization was performed by means of sealed opaque envelopes that contained the treatment option as derived from the computer-generated random numbers biased to allocate patients to control, high somatostatin dose, or terlipressin groups in a 1:3:3 ratio. Drug administration was performed under double-blind conditions and the code was not opened until all studies had been completed.

### Statistical Analysis

The sample size was calculated assuming standard deviations of HVPG changes ranging from 5% to 20% (9, 11, 17), and that a 10% reduction in HVPG would be clinically meaningful (11). Based on the plan to use a 2-tailed paired Student's *t* test, 20 patients were sufficient to detect this effect with a type I error of 0.05 and a power of 0.8.

Categorical variables were compared with the Fisher's exact test. Continuous variables, reported as mean  $\pm$  standard deviation (SD), were compared using the Student's *t* test for paired data within each group. Comparisons between groups were performed by the unpaired Student's *t* test with Bonferroni correction for multiple comparisons or with the nonparametric Mann-Whitney rank-sum test. Associations between variables were determined using Pearson's correlation coefficients. Significance was established at  $p < 0.05$ . All *p* values were 2-tailed. Results are expressed as mean  $\pm$  SD except when otherwise stated. Calculations were performed with the SPSS 10.0 statistical package (SPSS, Chicago, IL).

**Table 1.** Baseline Characteristics of Hemodynamic Responders and Poor Responders to the Usual Dose of Somatostatin<sup>a</sup>

	Responders to Somatostatin	Poor-Responders to Somatostatin
No. of cases	31	49
Sex (M/F)	19 (61%)/12 (39%)	33 (67%)/16 (33%)
Age (yr)	58 ± 13	61 ± 11
Alcoholic cirrhosis	18 (58%)	30 (61%)
Previous bleeding	10 (32%)	17 (35%)
Ascites	20 (64%)	29 (59%)
Encephalopathy	6 (19%)	10 (20%)
Albumin (g/L)	25 ± 4	27 ± 4
Bilirubin (μmol/L)	51 ± 43	47 ± 37
Prothrombin activity (%)	62 ± 13	63 ± 13
Creatinine (μmol/L)	100 ± 33	89 ± 35
Hemoglobin (g/dL)	7.8 ± 1.8	8.3 ± 1.7
Child-Pugh class (A/B/C)	3/19/9	8/33/8
Child-Pugh score (points)	8.7 ± 1.9	8.0 ± 1.8
Hypovolemic shock	9 (29%)	12 (24%)
Active bleeding at endoscopy	10 (32%)	14 (29%)
Infections <sup>b</sup>	7 (22%)	8 (16%)
Transfusion during the first 5 days (UPRC) <sup>c</sup>		
Mean	3.0 ± 2.8	2.9 ± 0.9
Median (range)	3 (0–11)	3 (0–11)
Intravenous fluid replacement during 24 h previous to hemodynamic study (L)	2.6 ± 0.5	2.9 ± 0.9
Interval admission—hemodynamic study (h)	60 ± 27	64 ± 22
Mean arterial pressure (mmHg)	83 ± 12	79 ± 10
Heart rate (beats/min)	86 ± 13	89 ± 15
Pulmonary wedge pressure (mmHg)	10.5 ± 4	9.7 ± 4
Right atrial pressure (mmHg)	6.1 ± 3	5.9 ± 3
Cardiac output (L/min)	8.9 ± 2.5	8.6 ± 2.5
HVPG (mmHg)	20.7 ± 4.2	21.6 ± 4.2

<sup>a</sup>Hemodynamic response to somatostatin was defined as a decrease of HVPG >10% from baseline or to <20 mmHg. No differences between groups were statistically significant.

<sup>b</sup>Bacterial infections diagnosed at admission or during the first 5 days.

<sup>c</sup>UPRC, units of packed red cells.

## RESULTS

Among 193 patients admitted to our unit with acute esophageal variceal bleeding from October 1999 to December 2002, 80 patients were included. The continuous infusion of 250 μg/h of somatostatin induced hemodynamic response in 31 (39%). All patients with a decrease in HVPG below 20 mmHg also had a reduction of >10% from baseline. There were no significant differences between responders and non-responders to somatostatin in relation to baseline clinical, biochemical, endoscopic, or hemodynamic data (Table 1). Among nonresponders, seven patients were allocated to the control group, 20 to the high somatostatin dose group, and 22 to the terlipressin group. Baseline data were similar in the three groups (Table 2).

### *Effects of Standard Continuous Infusion of Somatostatin*

In the total series of patients evaluated, 10 min after the start of the continuous infusion of 250 μg/h of somatostatin, there were no significant changes in HR or MAP, while HVPG significantly decreased (from 21.3 ± 4 to 19.2 ± 4 mmHg,  $p < 0.0001$ ). The decrease of HVPG was significantly greater in responders (from 20.7 ± 4 to 16.7 ± 3 mmHg) than in

nonresponders (from 21.6 ± 4 to 20.5 ± 4 mmHg,  $p < 0.001$  as compared with the final value in responders).

### *Hemodynamic Changes Observed in the Control Group*

In initial nonresponders to somatostatin, the maintenance of a continuous infusion of 250 μg/h of somatostatin for 30 min had no effects on systemic and splanchnic hemodynamics, as compared with changes observed 10 min after the start of infusion (Table 3).

### *Effects of High Infusion Dose of Somatostatin*

The continuous infusion of 500 μg/h of somatostatin caused a significant reduction in HR, while cardiopulmonary pressures increased (Table 3). The HVPG decreased significantly (Fig. 1), due to a reduction in WHVP and an increase in FHVP (Table 3). The rate of patients with a decrease in HVPG >10% from baseline was significantly higher than in the control group (Fig. 2).

### *Effects of Terlipressin*

Terlipressin induced a significant reduction of HR and cardiac output, and an increase of MAP and cardiopulmonary pressures (Table 3). The effect on MAP was greater than that observed with the high somatostatin dose (Table 3).

**Table 2.** Baseline Characteristics of Patients in Control Group, in Somatostatin 500  $\mu\text{g/h}$  Group, and in Terlipressin Group<sup>a</sup>

	Control (Somatostatin 250 $\mu\text{g/h}$ )	Somatostatin 500 $\mu\text{g/h}$	Terlipressin
No. of cases	7	20	22
Sex (M/F)	4 (57%)/3(43%)	13 (65%)/7 (35%)	16 (73%)/6 (27%)
Age (yr)	66 $\pm$ 9	62 $\pm$ 11	60 $\pm$ 11
Alcoholic cirrhosis	4 (57%)	14 (70%)	12 (55%)
Previous bleeding	1 (14%)	6 (30%)	10 (45%)
Ascites	2 (29%)	15 (75%)	12 (54%)
Encephalopathy	1 (14%)	4 (20%)	5 (23%)
Albumin (g/L)	28 $\pm$ 2	26 $\pm$ 3	28 $\pm$ 5
Bilirubin ( $\mu\text{mol/L}$ )	31 $\pm$ 18	51 $\pm$ 33	48 $\pm$ 43
Prothrombin activity (%)	60 $\pm$ 12	59 $\pm$ 11	67 $\pm$ 13
Creatinine ( $\mu\text{mol/L}$ )	115 $\pm$ 75	85 $\pm$ 31	84 $\pm$ 16
Hemoglobin (g/dL)	8.0 $\pm$ 1.3	8.1 $\pm$ 1.8	8.7 $\pm$ 1.8
Child-Pugh class (A/B/C)	2/4/1	1/17/2	5/12/5
Child-Pugh score (points)	7.7 $\pm$ 2.8	8.2 $\pm$ 1.4	7.9 $\pm$ 1.8
Hypovolemic shock	2 (29%)	5 (25%)	5 (23%)
Active bleeding at endoscopy	2 (29%)	5 (25%)	7 (32%)
Infections <sup>b</sup>	1 (14%)	3 (15%)	4 (18%)
Transfusion during the first 5 days (UPRC) <sup>c</sup>			
Mean	2.4 $\pm$ 2.1	3.8 $\pm$ 2.7	2.3 $\pm$ 2.3
Median (range)	2 (0–6)	3 (0–11)	2 (0–8)
Intravenous fluid replacement during 24 h previous to hemodynamic study (L)	2.5 $\pm$ 0.6	2.9 $\pm$ 0.6	3.1 $\pm$ 1.2
Interval admission—hemodynamic study (h)	61 $\pm$ 26	64 $\pm$ 23	66 $\pm$ 21

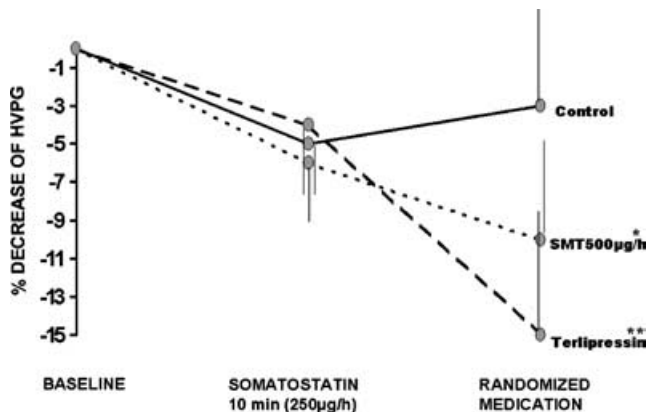
<sup>a</sup>No differences between groups were statistically significant.

<sup>b</sup>Bacterial infections diagnosed at admission or during the first 5 days.

<sup>c</sup>UPRC, units of packed red cells.

Terlipressin caused a significant decrease of HVPG (Fig. 1), due to a reduction in WHVP and an increase in FHVP (Table 3). The reduction in HVPG achieved by terlipressin was significantly greater than that observed with the high somatostatin dose (Fig. 1): the mean decrease in HVPG was of 15%  $\pm$  9% with terlipressin and of 10%  $\pm$  6% with the

high somatostatin dose ( $p = 0.05$ ). The rate of patients with a decrease in HVPG >10% from baseline value was greater with terlipressin than in the control group (Fig. 2). The rate of patients with a decrease in HVPG >20% was significantly higher with terlipressin than with the high somatostatin dose (Fig. 2).



**Figure 1.** Effects on HVPG in the three groups. Changes of HVPG 10 min after the initial administration of somatostatin (250  $\mu\text{g/h}$ ) with an initial bolus of 250  $\mu\text{g}$ , and 30 min after the administration of the randomized medication. Results are expressed as percentage of changes. \* $p < 0.001$  versus baseline, and  $p = 0.01$  as compared with the change in control group. \*\* $p < 0.001$  versus baseline,  $p < 0.001$  as compared with the change in control group, and  $p = 0.05$  as compared with the change in the group treated with the infusion of 500  $\mu\text{g/h}$  of somatostatin.

## DISCUSSION

Randomized controlled trials have adequately shown the efficacy of standard somatostatin infusion dose for the treatment of acute variceal bleeding, while its safety profile represents a major advantage over other vasoactive agents (10). In keeping with this, in the present study a standard infusion dose of somatostatin was used as a first-line therapy and nonresponders were subsequently randomized to receive an alternative treatment. The use of HVPG monitoring to assess hemodynamic response accurately stratifies the risk of an unfavorable outcome during acute variceal bleeding (23). Patients with an HVPG value below 20 mmHg and those in whom treatment induces a decrease >10% from baseline have a significantly better control of acute hemorrhage (11, 23). In the current study the majority of patients evaluated did not achieve these targets with the standard somatostatin infusion dose of 250  $\mu\text{g/h}$ . It should be emphasized that unfortunately, baseline clinical, biochemical, endoscopic, or hemodynamic data were not useful to identify the hemodynamic responders to standard somatostatin dose. This suggests that

**Table 3.** Splanchnic and Systemic Hemodynamics at Baseline, 10 Min after Somatostatin Administration (250  $\mu\text{g}/\text{h}$ ) and 30 Min after the Start of Randomized Medication, in Control Group, in Somatostatin 500  $\mu\text{g}/\text{h}$  Group, and in Terlipressin Group

	Baseline	Somatostatin	Randomized Medication
Control group (somatostatin 250 $\mu\text{g}/\text{h}$ ) (n = 7)			
MAP (mmHg)	82 $\pm$ 9	80 $\pm$ 10	82 $\pm$ 13
HR (beats/min)	95 $\pm$ 10	94 $\pm$ 10	98 $\pm$ 10
PWP (mmHg)	10.8 $\pm$ 6.5		12.1 $\pm$ 5.5
RAP (mmHg)	5.7 $\pm$ 2.5		6.8 $\pm$ 2.7 <sup>a</sup>
CO (L/min)	8.9 $\pm$ 2.4		8.9 $\pm$ 2.1
WHVP (mmHg)	31.1 $\pm$ 4.2	30.4 $\pm$ 3.7 <sup>b</sup>	30.6 $\pm$ 4.0
FHVP (mmHg)	11.8 $\pm$ 3.8	12.0 $\pm$ 3.8	11.8 $\pm$ 3.6
HVPG (mmHg)	19.3 $\pm$ 4.4	18.4 $\pm$ 4.5 <sup>a</sup>	18.7 $\pm$ 4.1
Somatostatin 500 $\mu\text{g}/\text{h}$ (n = 20)			
MAP (mmHg)	78 $\pm$ 8	76 $\pm$ 10	75 $\pm$ 10
HR (beats/min)	86 $\pm$ 16	83 $\pm$ 15 <sup>a</sup>	82 $\pm$ 15 <sup>b,c</sup>
PWP (mmHg)	10.3 $\pm$ 3.6		12.6 $\pm$ 2.8 <sup>b</sup>
RAP (mmHg)	6.0 $\pm$ 2.7		7.3 $\pm$ 2.3 <sup>b</sup>
CO (L/min)	8.9 $\pm$ 2.7		8.7 $\pm$ 2.8
WHVP (mmHg)	33.2 $\pm$ 4.9	32.2 $\pm$ 5.1 <sup>a</sup>	31.7 $\pm$ 4.8 <sup>a</sup>
FHVP (mmHg)	11.4 $\pm$ 3.2	11.6 $\pm$ 3.2	12.4 $\pm$ 2.9 <sup>b</sup>
HVPG (mmHg)	21.8 $\pm$ 3.4	20.5 $\pm$ 3.2 <sup>b</sup>	19.6 $\pm$ 3.1 <sup>b</sup>
Terlipressin (n = 22)			
MAP (mmHg)	79 $\pm$ 11	79 $\pm$ 10	88 $\pm$ 13 <sup>b,d</sup>
HR (beats/min)	90 $\pm$ 15	87 $\pm$ 15 <sup>b</sup>	79 $\pm$ 15 <sup>b,c</sup>
PWP (mmHg)	9.2 $\pm$ 4.0		14.9 $\pm$ 6.1 <sup>b,d</sup>
RAP (mmHg)	4.9 $\pm$ 2.8		8.1 $\pm$ 3.5 <sup>b,d</sup>
CO (L/min)	8.2 $\pm$ 2.1		7.4 $\pm$ 2.6
WHVP (mmHg)	32.6 $\pm$ 5.5	31.8 $\pm$ 5.4 <sup>b</sup>	31.3 $\pm$ 5.8 <sup>a</sup>
FHVP (mmHg)	10.4 $\pm$ 3.6	10.7 $\pm$ 3.4	12.3 $\pm$ 3.8 <sup>b</sup>
HVPG (mmHg)	22.2 $\pm$ 5.0	21.1 $\pm$ 4.9 <sup>b</sup>	19.1 $\pm$ 5.2 <sup>b,d</sup>

MAP, mean arterial pressure; HR, heart rate; PWP, pulmonary wedge pressure; RAP, right atrial pressure; CO, cardiac output; WHVP, wedged hepatic venous pressure; FHVP, free HVP; and HVPG, hepatic venous pressure gradient.

<sup>a</sup> $p < 0.05$ , within group variation, compared with baseline.

<sup>b</sup> $p < 0.01$ , within group variation, compared with baseline.

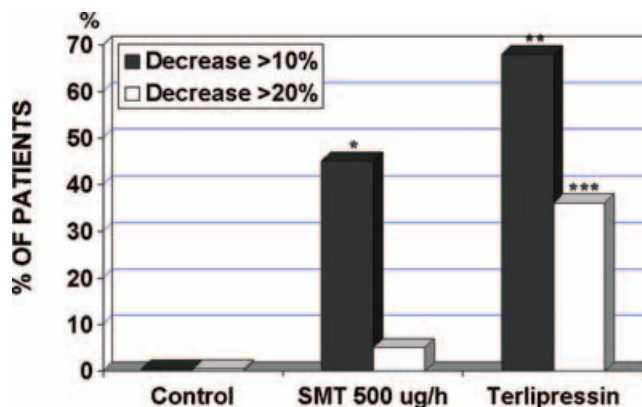
<sup>c</sup> $p < 0.05$ , for the comparison with the control group.

<sup>d</sup> $p < 0.05$ , for the comparison with the change observed in somatostatin 500  $\mu\text{g}/\text{h}$  group.

at present, only HVPG monitoring may provide such prognostic information to predict the failure to control acute variceal bleeding.

The results of the present study clearly show that both terlipressin and the high somatostatin infusion dose of 500  $\mu\text{g}/\text{h}$  significantly decreased the HVPG in previous nonresponders to a standard somatostatin dose of 250  $\mu\text{g}/\text{h}$ . Both treatments achieved a high rate of hemodynamic responders, significantly greater than that observed among patients in the control group.

The marked hemodynamic effect obtained in this study with the high somatostatin infusion dose is not surprising. Previous studies have shown that such a high somatostatin dose is associated with a more pronounced hemodynamic effect than that observed with the usual infusion dose (9). Furthermore, it has been suggested that the use of high dose of somatostatin infusion translates into an increased clinical efficacy to control variceal bleeding, particularly when active hemorrhage is found at emergency endoscopy (24).



**Figure 2.** Hemodynamic response in the three groups. A decrease of HVPG  $>10\%$  from baseline was achieved in none of the seven patients of the control group, in 9 of the 20 patients treated with the infusion of 500  $\mu\text{g}/\text{h}$  of somatostatin, and in 15 of the 22 patients treated with terlipressin. A decrease of HVPG  $>20\%$  from baseline was achieved in one patient treated with 500  $\mu\text{g}/\text{h}$  of somatostatin and in eight patients treated with terlipressin. Results are expressed as percent of patients. \* $p = 0.05$  as compared with the control group. \*\* $p = 0.002$  as compared with the control group. \*\*\* $p = 0.02$  as compared with the group treated with the infusion of 500  $\mu\text{g}/\text{h}$  of somatostatin.

What may occur using octreotide cannot be inferred from these results. Contrasting effects on portal pressure have been achieved with octreotide, although the HVPG did not decrease in most studies using different doses (10). Somatostatin analogues have different receptor affinities as compared with the natural compound, which may help to explain the slightly different effects of somatostatin and octreotide on HVPG. Moreover, a rapid desensitization to the effects of octreotide has been described (25). Because of this repeated bolus of this analogue achieves less effect on HVPG, and injecting a higher dose does not increase or prolong the effect (25).

Terlipressin, or triglycyl-lysine vasopressin, is a synthetic vasopressin analogue with intrinsic vasoactive activity, which is slowly transformed into vasopressin by enzymatic cleavage of the glycyl residues (26, 27). This results in a continuous release of small amounts of vasopressin and in prolonged biological effects with fewer complications (28). Hemodynamic studies have shown that terlipressin has a marked and significant effect decreasing portal pressure, portocollateral blood flow, and variceal pressure (15–19, 29, 30). The magnitude of the decrease in portal pressure achieved in studies using terlipressin seems markedly greater than that reported in studies using somatostatin. Indeed, this was the case when terlipressin was compared with octreotide in portal hypertensive rats (31). However, the hemodynamic effects of terlipressin and somatostatin have not been directly compared in humans. It must be noted that the present study showed that terlipressin significantly reduced HVPG in patients who did not respond to the usual somatostatin infusion dose. This portal hypotensive effect was even greater than that

observed with the high somatostatin infusion dose in these patients.

The apparently greater portal hypotensive effect of terlipressin as compared with somatostatin has not been shown to translate into a higher clinical efficacy for the treatment of acute variceal bleeding (1). This may seem surprising, taking into account the higher reduction of portal pressure achieved with terlipressin. However, it must be noted that besides the effect on portal pressure, recent studies have shown that somatostatin has additional effects that may help to explain its clinical efficacy, and which are probably linked to the prevention of the release of vasoactive peptides induced by this drug (11). Somatostatin infusion has been shown to prevent secondary rises of portal pressure during the acute bleeding episode, such as those induced by the presence of blood in the gastrointestinal tract or by volume restitution (8, 11). This stabilization of portal pressure may reduce the risk of further hemorrhage, and thus may account for the clinical efficacy achieved with this therapy.

According to the above considerations, several issues deserve further comment. Although the standard infusion dose of somatostatin is an effective first-line treatment for variceal bleeding with a very good safety profile, therapeutic failure occurs in as many as 20–40% of cases. The results of the current study suggest that both terlipressin and high somatostatin infusion dose may be valuable alternatives when the standard dose of somatostatin fails. However, the value of this strategy in clinical practice should be addressed in specifically designed randomized controlled trials. Another issue to consider is whether the combined administration of terlipressin and somatostatin may increase the efficacy of pharmacological treatment for acute variceal bleeding. This combined therapy may attack the problem at different levels, and take advantage of the beneficial effects of both drugs, as suggested in experimental studies (31, 32). On one hand, this combination may benefit from the greater portal hypotensive effect achieved with terlipressin, and on the other hand from the preventive effect of somatostatin avoiding secondary increases in portal pressure during the course of the acute bleeding episode. Furthermore, recent *in vitro* studies have shown that octreotide, a somatostatin analogue, potentiates the effects of protein kinase C-dependent vasoconstrictors (14). This suggests that somatostatin may also enhance the vasoconstrictive effect induced by terlipressin. However, the efficacy and safety of this combined therapy should also be adequately addressed in future randomized controlled trials.

In summary, this study has shown that both terlipressin and a high infusion dose of somatostatin of 500  $\mu\text{g/h}$  significantly decrease portal pressure in a high-risk subset of patients who do not respond to the standard 250  $\mu\text{g/h}$  dose of somatostatin. Both treatments significantly increased the rate of patients with a reduction in HVPG > 10%, while terlipressin achieved a decrease in HVPG > 20% more frequently than the high dose of somatostatin.

## ACKNOWLEDGMENTS

We thank Montse Valdearcos and Josep Segret for their excellent technical support and the nursing and medical Staff of the Gastrointestinal Bleeding Unit and Semicritics Unit of the Hospital de la Santa Creu i Sant Pau for their cooperation in this study.

---

**Reprint requests and correspondence:** Cándid Villanueva, M.D., Servei de Patologia Digestiva, Hospital de la Santa Creu i Sant Pau, Avda. Sant Antoni M<sup>a</sup> Claret, 167, Barcelona 08025, Spain.  
Received July 1, 2004; accepted July 9, 2004.

---

## REFERENCES

1. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: An evidence-based approach. *Semin Liver Dis* 1999;19:475–505.
2. Villanueva C, Ortiz J, Sàbat M, et al. Somatostatin alone or combined with emergency sclerotherapy in the treatment of acute esophageal variceal bleeding: A prospective randomized trial. *Hepatology* 1999;30:384–9.
3. Bosch J, Kravetz D, Rodes J. Effects of somatostatin on hepatic and systemic hemodynamics in patients with cirrhosis of the liver. Comparison with vasopressin. *Gastroenterology* 1981;80:518–25.
4. Eriksson LS, Law DH, Wahren J. Influence of somatostatin on splanchnic haemodynamics in patients with liver cirrhosis. *Clin Physiol* 1984;4:5–11.
5. Sonnenberg GE, Keller U, Perruchud A, et al. Effect of somatostatin on splanchnic haemodynamics in patients with cirrhosis of the liver and in normal subjects. *Gastroenterology* 1981;80:526–32.
6. Merkel C, Gatta A, Zuin R, et al. Effects of somatostatin on splanchnic haemodynamics in patients with liver cirrhosis and portal hypertension. *Digestion* 1985;32:92–8.
7. Polio J, Groszmann RJ. Hemodynamic factors involved in the development and rupture of esophageal varices: A pathophysiologic approach to treatment. *Semin Liver Dis* 1986;6:318–31.
8. McCormick PA, Jenkins SA, McIntyre N, et al. Why portal hypertensive varices bleed and bleed: A hypothesis. *Gut* 1995;36:100–103.
9. Cirera I, Feu F, Luca A, et al. Effects of bolus injections and continuous infusions of somatostatin and placebo in patients with cirrhosis. A double-blind hemodynamic investigation. *Hepatology* 1995;22:106–11.
10. Abraldes JG, Bosch J. Somatostatin and analogues in portal hypertension. *Hepatology* 2002;35:1305–12.
11. Villanueva C, Ortiz J, Miñana J, et al. Somatostatin treatment and risk stratification by continuous portal pressure monitoring during acute variceal bleeding. *Gastroenterology* 2001;121:110–7.
12. Sieber CC, Mosca PG, Groszmann RJ. Effect of somatostatin on mesenteric vascular resistance in normal and portal hypertensive rats. *Am J Physiol* 1992;262(Suppl):G274–7.
13. Chatila R, Ferayorni L, Grupta TK, et al. Local arterial vasoconstriction induced by octreotide in patients with cirrhosis. *Hepatology* 2000;31:572–6.
14. Wiest R, Tsai MH, Groszmann RJ. Octreotide potentiates PKC-dependent vasoconstrictors in portal-hypertensive and control rats. *Gastroenterology* 2001;120:975–83.

15. Merkel C, Gatta A, Bolognesi M, et al. Hemodynamic changes of systemic, hepatic, and splenic circulation following triglycyl-lysine-vasopressin administration in alcoholic cirrhosis. *Dig Dis Sci* 1988;33:1103–9.
16. Nevens F, Van Steenberghe W, Yap SH, et al. Assessment of variceal pressure by continuous non-invasive endoscopic registration: A placebo controlled evaluation of the effect of terlipressin and octreotide. *Gut* 1996;38:129–34.
17. Escorsell A, Bandi JC, Moitinho E, et al. Time profile of the hemodynamic effects of terlipressin in portal hypertension. *J Hepatol* 1997;26:621–7.
18. Romero G, Kravetz D, Argonz J, et al. Terlipressin is more effective in decreasing variceal pressure than portal pressure in cirrhotic patients. *J Hepatol* 2000;32:419–25.
19. Møller S, Hansen EF, Becker U, et al. Central and systemic haemodynamic effects of terlipressin in portal hypertensive patients. *Liver* 2000;20:51–9.
20. Kravetz D, Cummings SA, Groszmann RJ. Hyposensitivity to vasopressin in a hemorrhaged-transfused rat model of portal hypertension. *Gastroenterology* 1988;93:170–5.
21. Tsai YT, Lee FY, Lin HC, et al. Hyposensitivity to vasopressin in patients with hepatitis B-related cirrhosis during acute variceal hemorrhage. *Hepatology* 1991;13:407–12.
22. Moitinho E, Escorsell A, Bandi JC, et al. Somatostatin is less effective decreasing portal pressure during acute variceal bleeding than in stable conditions [Abstract]. *J Hepatol* 1998;28:74.
23. Moitinho E, Escorsell A, Bandi JC, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology* 1999;117:626–31.
24. Moitinho E, Planas R, Bañares R, et al. Multicenter randomized controlled trial comparing different schedules of somatostatin in the treatment of acute variceal bleeding. *J Hepatol* 2001;35:712–8.
25. Escorsell A, Bandi JC, Andreu V, et al. Desensitization to the effects of intravenous octreotide in cirrhotic patients with portal hypertension. *Gastroenterology* 2001;120:161–9.
26. Nilsson G, Lindblom P, Ohlin M, et al. Pharmacokinetic of terlipressin after single iv doses to healthy volunteers. *Drugs Exp Clin Res* 1990;6:307–14.
27. Forsling ML, Aziz LA, Miller M, et al. Conversion of triglycyl-vasopressin to lysine-vasopressin in man. *J Endocrinol* 1980;85:237–44.
28. Blei AT. Vasopressin and analogs in portal hypertension. Different molecules but similar questions. *Hepatology* 1986;6:146–7.
29. Vosmik J, Jedlicka K, Mulder JL, et al. Action of the triglycyl hormonogen of vasopressin (glypressin) in patients with liver cirrhosis and bleeding esophageal varices. *Gastroenterology* 1977;72:605–9.
30. Lin HC, Tsai YT, Lee FY, et al. Systemic and portal haemodynamic changes following triglycyl-lysine-vasopressin plus nitroglycerin administration in patients with hepatitis B related cirrhosis. *J Hepatol* 1990;10:370–4.
31. Oberti F, Veal N, Kaassis M, et al. Hemodynamic effects of terlipressin and octreotide administration alone or in combination in portal hypertensive rats. *J Hepatol* 1998;29:103–11.
32. Moreau R, Cailmail S, Valla D, et al. Haemodynamic responses to a combination of terlipressin and octreotide in portal hypertensive rats. *Aliment Pharmacol Ther* 1997;11:993–7.