Randomized Controlled Trial of Desmopressin Plus Terlipressin vs. Terlipressin Alone for the Treatment of Acute Variceal Hemorrhage in Cirrhotic Patients: A Multicenter, Double-blind Study

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1-Deamino-8-D-arginine vasopressin (DDAVP, desmopressin), a synthetic analog of the antidiuretic hormone L-arginine vasopressin, improves hemostasis parameters in cirrhotic patients. Hence its use in combination with a vasoactive drug such as terlipressin might improve the performance of this drug in controlling variceal bleeding. The aim of this trial was to compare the efficacy of desmopressin plus terlipressin with that of terlipressin alone in controlling acute variceal hemorrhage. Cirrhotic patients with active variceal hemorrhage diagnosed endoscopically were randomized within 2 hr of admission to receive desmopressin plus terlipressin or placebo plus terlipressin. Terlipressin (2 mg, intravenous bolus) was given at time 0 and every 4 hr thereafter for 24 hr. Desmopressin (0.3 μg/kg, intravenously) or placebo was given in saline solution over 30 min at time 0 and at 26 hr. Patients were monitored for 24 hr after cessation of treatment. Treatment failure was defined as recurrence of active bleeding during treatment or within the 24 hr after treatment. After enrolling 51 of the planned 84 patients, we carried out an interim analysis. Treatment failure occurred in 13 of 24 patients randomized to receive desmopressin plus terlipressin (54.2%) and in 6 of 22 patients randomized to receive terlipressin (27.3%) (p = 0.06, Fisher's exact test). The trial was interrupted at this stage because patients treated with the "new" therapy fared worse than those treated with the standard therapy, and the possibility of reversing this trend by completing the trial was deemed remote. The addition of desmopressin does not improve and may worsen the efficacy of terlipressin in controlling acute variceal bleeding in cirrhotic patients. (HEPATOLOGY 1993;18:1102-1107.)

Cirrhotic patients who bleed from ruptured esophageal varices are managed with a variety of treatments (i.e. emergency endoscopic sclerotherapy, balloon tamponade, vasoactive drugs). Although some studies have shown that sclerotherapy can be lifesaving (1, 2), the superiority of this technique over other treatment modalities has not been univocally proven. In addition, emergency sclerotherapy requires a skilled endoscopist; as a result, this procedure is available 24 hr a day in only a few centers. Thus a safe and effective medical regimen to treat acute variceal hemorrhage is still desirable. Such a form of treatment might be used alone or as a time-buying measure while emergency sclerotherapy is being organized. Vasoconstrictors such as vasopressin and somatostatin (3-6), used to treat variceal hemorrhage, achieve complete control of bleeding only in about 50% to 60% of patients (7); repeat bleeding often occurs during the treatment period (7) or shortly after discontinuation of the drugs. Two recent placebo-controlled studies have reported complete control of bleeding in 60% and 90% of patients with terlipressin (triglycil lysil-vasopressin, a recently introduced, longer-acting vasopressin analog) (8, 9). Besides portal hypertension, many cirrhotic patients have complex disorders of primary hemostasis and of blood coagulation. Little is known about the influence of these clotting disorders on the acute bleeding episode; they have never been assessed in bleeding cirrhotic patients. However, attempts to correct these disorders with fresh frozen plasma, platelet concentrates and prothrombin complex concentrates have failed to gain widespread acceptance because these blood products are of unproven efficacy and can transmit blood-borne infections and induce thrombosis. Non-

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transfusional forms of treatment of hemostatic defects would be desirable. Of the current medical alternatives to endoscopic variceal sclerotherapy, vasopressin induces transient increases of some clotting factors (10, 11), and terlipressin (12) and somatostatin have no effect. On the other hand, 1-deamino-8-D-arginine vasopressin (DDAVP, desmopressin), a synthetic analog of the antidiuretic hormone L-arginine vasopressin, shortens bleeding time (a measure of primary hemostasis) and partial thromboplastin time (a measure of intrinsic coagulation) and increases levels of factor VIII and von Willebrand factor in cirrhotic patients for 4 to 6 hr after its intravenous infusion (13-14). In addition, DDAVP has been successfully used as a nonspecific hemostatic agent to reduce blood loss during surgery in patients with normal hemostatic function (15, 16). Hence DDAVP might be a useful adjunct to the medical treatment of variceal hemorrhage in cirrhotic patients. The use of this hemostatic drug in combination with drugs that lower portal pressure might improve their performance in achieving complete control of variceal bleeding. Such an improvement might be a result of an increased success rate in the initial control of bleeding or of a decrease in the incidence of early repeat bleeding (i.e., during the first 24 hr after cessation of treatment), which is one of the weaknesses of vasoactive drugs used in this setting.

The aim of this trial was to compare the efficacy of DDAVP plus terlipressin with that of terlipressin alone in controlling acute variceal hemorrhage in cirrhotic patients.

PATIENTS AND METHODS

Trial Design. The trial was carried out in double-blind, randomized, controlled multicenter fashion. The time frame during which the effectiveness of treatments in controlling hemorrhage was evaluated was 50 hr (treatment period of 26 hr followed by an observation period of 24 hr). After the observation period, the patients were allowed to undergo other treatments aimed at preventing further variceal bleeding (long-term endoscopic variceal sclerotherapy, β-blockers or surgery).

Criteria for Admission. All patients admitted to the participating institutions for active upper-gastrointestinal hemorrhage were eligible for the study if they met several criteria. First, emergency endoscopy had to show unequivocal signs of active variceal bleeding (blood spurting or oozing from a varix). If stigmata of recent variceal bleeding ("coffee grounds" in the stomach plus a clot on a varix) were seen, the patient was not eligible for study unless bleeding resumed (i.e., if nasogastric tube effluent became bright red within 24 hr). If emergency endoscopy could not be carried out within 2 hr of admission, patients were still eligible for the study if they met the following criteria: (a) They already had been found to have cirrhosis on the basis of history, physical examination, liver chemistries and/or liver histology and were known to have varices or (b) they showed physical signs (hepatomegaly, ascites, jaundice, vascular spiders, asterixis) strongly suggesting a diagnosis of cirrhosis and (c) they showed unequivocal signs of active upper gastrointestinal bleeding (see above). In these patients, elective endoscopy was performed within 24 hr of randomization.

If a patient was unable to give informed consent, a relative was required to do so.

The study protocol was approved by the Human Research Review Committee of every center involved in the study.

Exclusion Criteria. Patients were not eligible for the study if they had undergone therapy with endoscopic variceal sclerotherapy or β-blockers because we felt that bleeding might be different (i.e., less severe or more difficult to control) in these patients, thus introducing potential bias in the results. In addition, patients previously treated with portal-decompressive surgery, patients in whom a nasogastric tube could not be placed on admission, patients with anuria (empty bladder at catheterization) and patients with histories of ischemic heart disease (potential complications from vasoconstrictor drugs and drugs to enhance coagulation) were not enrolled in the trial.

Randomization and Treatment Schedule. Eligible patients were randomized within 2 hr of admission. Randomization was carried out in blocks of four (i.e., the test substance was DDAVP in two cases and placebo in the other two). Patients were randomized to receive one of the following treatments. Treatment A was terlipressin (2 mg, intravenously, given as a bolus over 3 min) at time 0 and at 4, 8, 12, 16, 20 and 24 hr; and DDAVP (0.3 μg/kg, intravenously, given in 50 ml saline solution over 30 min) at time 0 and at 26 hr. Treatment B was terlipressin (2 mg, intravenously, given in bolus over 3 min) at time 0 and at 4, 8, 12, 16, 20 and 24 hr; and placebo (50 ml saline solution, given over 30 min) at time 0 and at 26 hr.

Ancillary Treatment. Patients in both groups were allowed blood transfusions, intravenous fluids, oral antacids, neomycin and lactulose as required by their clinical conditions. The use of blood products such as fresh frozen plasma or platelet concentrates was not allowed.

Blindness. The drugs under trial were prepackaged and numbered for each patient before the time of randomization by Ferring AB (Malmoe, Sweden). Each package contained the amount of drugs, either terlipressin and DDAVP or terlipressin and placebo (identical to DDAVP) needed to treat a single patient. Because DDAVP causes transient flushing lasting about 20 min after the administration of the drug, the physicians in charge of the assessment of the results of treatment were not allowed to see the patients for 1 hr after the administration of DDAVP or placebo. During this time, the patients were managed only by the staff member in charge of the administration of the trial drugs.

Baseline Clinical Assessment. At entry, a full medical history and a physical examination—including EKG, clinical laboratory determinations including measures in blood chemistry (total protein, serum protein electrophoresis, creatinine, urea nitrogen, direct and total bilirubin, AST, ALT, alkaline phosphatase, blood glucose, sodium and potassium chloride, blood ammonia), urinalysis, plasma osmolarity, hematological indexes (hematocrit, hemoglobin, complete blood count including differential) and prothrombin time—were obtained. The degree of hepatic decompensation was assessed according to Child's classification modified according to Pugh's criteria (17).

Patient Management and Follow-up. On admission, every patient was fitted with a nasogastric tube. The stomach was emptied, and gastric content was assessed and recorded every 2 hr. The nasogastric tube was kept in place for 50 hr. Control of hemorrhage and recurrent hemorrhage were evaluated as defined below under "Definitions of Control of Bleeding and Treatment Failure." Transfusion requirements were recorded. Urinary output was checked hourly, and the hematocrit was measured every 3 hr. Complete blood counts and

TABLE 1. Features of patients at entry

Features	DDAVP plus terlipressin	Terlipressin plus placebo
No. of patients	24	22
Mean age (yr)	56	59
Sex (M/F)	18/6	14/8
Pathogenesis (% alcoholic)	66.6	45
Child class (A/B/C)	9/12/3	8/8/6
Ascites (%)	62	63
Encephalopathy (%)	29	36
Mean hematocrit (%)	26	29
Mean BUN (gm/L)	0.7	0.7
Mean systolic blood pressure (mm Hg)	124	121

Differences between groups not statistically significant.

assays of blood urea nitrogen, plasma electrolytes, plasma osmolarity and serum creatinine were performed twice daily. Urinary electrolytes and urinary osmolarity were checked daily.

The outcomes of patients up to wk 6 after the end of the study period was also checked.

Definition of Control of Bleeding and Treatment Failure. We assumed that bleeding was controlled when the effluent of the nasogastric tube became clear and remained so during gastric lavage for at least 4 hr. Definitive control of bleeding was considered the persistence of clear effluent from the nasogastric tube for 24 hr after discontinuation of treatment. Recurrent bleeding was defined as the reappearance of red or maroon effluent from the nasogastric tube, persisting despite gastric lavage and not turning clear after lavage with 2 L of water, with instability of vital signs, hematocrit, hemoglobin or all three.

Treatment failure was defined as the persistence or the recurrence of active bleeding during the treatment or the observation period, regardless of the need for alternative therapy (Sengstaken-Blakemore tamponade, endoscopic sclerotherapy or emergency portacaval shunt).

Criteria for Removal of Patients from the Trial. It was agreed that participation of a patient in the trial would be discontinued if serious adverse reactions developed while the patient was under treatment, provided the investigators were convinced that such reactions could be attributed to the drugs under trial. In addition, if a patient was included in the trial with a presumptive diagnosis of cirrhosis and subsequent clinical testing revealed that the patient had no cirrhosis, the patient was excluded from analysis. Finally, if endoscopy performed within 24 hr of the beginning of treatment showed that a patient was bleeding from a source other than a varix, he or she was excluded from analysis.

Sample Size and Statistical Analysis. Assuming that terlipressin alone may be expected to achieve definitive control of variceal hemorrhage in about 55% of patients and that DDAVP plus terlipressin might control hemorrhage in another 30% of patients, about 37 patients per group were judged necessary to give the study an alpha error of 0.05 and a power of 80%. Allowing for 10% rate of exclusions in each group, we planned to enroll 41 or 42 patients per group and to carry out an interim analysis after 25 patients per group had been enrolled to determine the number of patients required to achieve statistical significance. The primary endpoint of the study was the definitive control of bleeding. Secondary endpoints were the initial control of bleeding (i.e., the number of patients in whom bleeding stopped at least temporarily during treatment) and transfusion requirements. The distribution of prognostic variables in the two treatment groups was analyzed with the χ^2 test and Student's t test as appropriate. Rates of bleeding control and treatment failure were assayed by means of life-table analysis. The crude number of events was compared in a contingency table by means of Fisher's exact test. Continuous parameters such as duration of bleeding and transfusion requirements were analyzed with Student's t test, the Mann-Whitney U test and the Wilcoxon's test for unpaired data as appropriate. The statistician was kept blind to the treatments received by patients throughout the interim analysis.

It was decided that the study would be interrupted after the interim analysis if the results of the latter showed a trend against the "new" treatment that could not be reversed by completion of the trial.

RESULTS

Seven centers participated in the study. Between December 1989 and April 1991, 145 patients were considered as candidates for the study. Of these, 94 were excluded. In 90 cases, the reason for exclusion was previous treatment with sclerotherapy or β-blockers. Four patients were not enrolled because they were in such poor condition as to prevent the placement of a nasogastric tube and died shortly after. Fifty-one patients were eligible and were enrolled in the trial. Twenty-six were randomized to receive DDAVP plus terlipressin; 25 were given placebo plus terlipressin. The seven centers enrolled 17, 10, 6, 6, 5, 5 and 2 patients. Two patients in the placebo plus terlipressin group and three in the DDAVP plus terlipressin group did not fulfill the criteria of admission and were thus excluded from interim analysis. Reasons for exclusion were bleeding from sources other than varices in four (three from hemorrhagic gastritis, one from duodenal ulcer) and bleeding from an unknown site in one patient who had no endoscopic evidence of esophageal or gastric varices. In all the remaining patients emergency endoscopy confirmed the presence of active variceal bleeding. Therefore 46 patients entered the interim analysis; 24 in the DDAVP plus terlipressin group and 22 in the terlipressin group.

Table 1 shows the main demographic, clinical and biochemical features of the patients at entry. The two groups were evenly balanced in age, sex distribution, pathogenesis of cirrhosis, degree of liver decompensation and clinical and biochemical parameters. None of the patients had to be removed from the study because of adverse reaction to the drug treatment.

Assessment of Clinical and Biochemical Parameters During Follow-up. Clinical and biochemical parameters during follow-up were similar in the two groups. In particular, heart rate, blood pressure, urinary output, plasma electrolytes and plasma osmolarity were not significantly different between groups throughout follow-up.

Initial Control of Bleeding. Bleeding was initially controlled in 16 patients (66.7%) in the terlipressin plus

DDAVP group and in 18 patients (81.8%) in the terlipressin group. The difference between the two groups was not statistically significant (rate of difference, −15.1%; 95% confidence interval, −40.6% to 10.3%).

Definitive Control of Bleeding. Definitive control of bleeding was achieved in 11 patients in the DDAVP plus terlipressin group (45.8%) and in 16 patients in the terlipressin group (72.7%). The difference approached statistical significance (rate of difference, −26.9%; 95% confidence interval, −54.4% to 1.6%; one-sided Fisher's exact test, p = 0.06 binomial estimate of power to detect such a difference with an α error of 0.05, 0.30).

Handling of Treatment Failure. Treatment failure occurred in 13 of the 24 patients randomized to DDAVP plus terlipressin and in 6 of the 22 patients randomized to placebo plus terlipressin (54.1% and 26.6%, respectively; rate of difference, 26.9%; 95% confidence interval, −1.6% to 55.4%). Of these, 11 in the former group and 5 in the latter had to be treated with alternative therapies. These therapies are reported in Table 2. The Kaplan-Meier curves of treatment failures in the two groups are shown in Figure 1.

Transfusion Requirements. The mean number of units of blood transfused was 3.6 (range = 0 to 10 units) in the DDAVP plus terlipressin group and 4.3 (range = 0 to 11 units) in the terlipressin group. The difference was not statistically significant (Table 3). The median numbers of units transfused per hour in patients of the two groups were also similar.

Deaths. Four patients in the DDAVP plus terlipressin group (16.7%) and two in the terlipressin group (9.1%) died of massive hemorrhage despite treatment with alternative therapies. The difference was not statistically significant (rate of difference, 7.6%; 95% confidence interval, −11.9% to 27.1%).

Termination of the Study. The study was terminated after the interim analysis because patients treated with the new therapy fared worse than those treated with the standard therapy. Although the difference between the two groups in terms of treatment failure was not statistically significant, the direction of the effect of the new therapy was opposite what we expected. At this point in the study, the possibility of reversing this trend was deemed extremely remote.

Patient Outcome 6 Wk After the End of the Study Period. Of 20 patients in the DDAVP plus terlipressin group who survived the study period, 8 (40%) were alive and free of bleeding at 6 wk, 4 (20%) had repeat bleeding but survived at wk 6, 1 (5%) had repeat bleeding and died of hemorrhage, 1 (5%) died of liver failure, and 6 (30%) were lost to follow-up. Of the 20 patients in the terlipressin group who survived the study period, 7 (35%) were alive and free of repeat bleeding at 6 wk, 5 (25%) had repeat bleeding but survived at 6 wk, 4 (20%) had repeat bleeding and died, 1 (5%) died of liver failure and 1 (5%) was lost to follow-up. The differences between groups were not statistically significant.

Adjustment for Imbalance. Adjustment for imbalance in prognostic variables was performed with Cox regression analysis in which the prognostic variables were included together with the treatment variable. In addition to treatment, the final Cox regression model included the pathogenesis of cirrhosis, Child class and age. In this analysis, the strong trend in favor of terlipressin alone persisted but was not statistically significant.

TABLE 2. Alternative treatments used in patients in whom treatment failed

Treatment	DDAVP plus terlipressin	Terlipressin plus placebo
Sclerotherapy	6	3
Sclerotherapy + Sengstaken tube	1	1
Sengstaken tabe	3	0
Sclerotherapy + Sengstaken tube + somatostatin	0	1
Sengstaken tube + somatostatin	1	0
Supportive measures only	2	1

DISCUSSION

In this study, we attempted to improve the performance of vasoactive drugs in controlling variceal hemorrhage in cirrhotic patients by improving the hemostasis abnormalities that are present in these patients and may contribute to initiation or maintenance of variceal hemorrhage. Therefore we compared a standard treatment with terlipressin with a combination of terlipressin plus DDAVP, which is an effective nonspecific hemostatic agent (15, 16) that has been shown to improve the bleeding and partial thromboplastin times in cirrhotics for 4 to 6 hr after intravenous infusion (13, 14).

Patients were randomized within 2 hr of admission because the treatment under trial, if proved effective, would be proposed as a first therapeutic maneuver in all patients with variceal bleeding, regardless of the subsequent therapies to be employed. Therefore it was deemed important to test the treatment under the very same conditions of its intended use in clinical practice. The efficacy of treatment was evaluated over 50 hr: a treatment period of 26 hr followed by an observation period of 24 hr. The study was designed with a posttreatment observation period of 24 hr because the main limit of vasoactive drugs is the high incidence of early repeat bleeding after discontinuation of treatment, and we wanted to ascertain whether the addition of DDAVP might improve this drawback.

Terlipressin alone was very effective in controlling variceal hemorrhage, achieving definitive control of bleeding in over 70% of the patients. This figure closely matches the results of the study by Soederlund et al. (9), which are the best ever obtained with vasoactive drugs alone. Our data, together with those by Soederlund, indicate that terlipressin alone is effective not only for the immediate control of variceal bleeding but is also

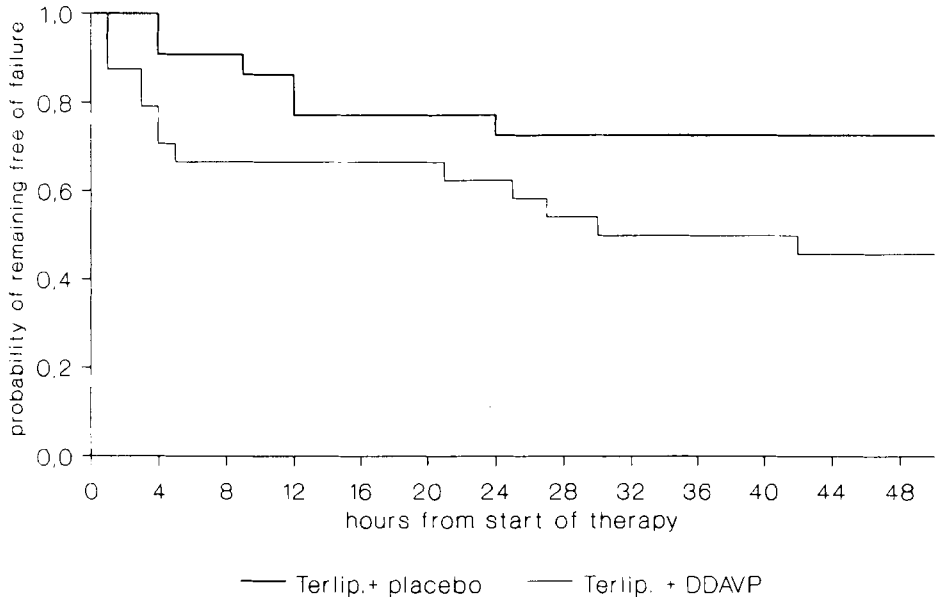

FIG. 1. Time elapsed before treatment failure.

TABLE 3. Transfusion requirements

Group	Total no. of units		p Value
	DDAVP plus terlipressin	Terlipressin plus placebo	
All patients	3.6 ± 2.8 (0-10)[a]	4.3 ± 2.7 (0-11)	NS
Treatment failures	2.8 ± 1.7 (0-5)	3.4 ± 2.3 (0-8)	NS

[a]Data expressed as mean ± S.D. (range).

capable of achieving definitive control of bleeding for up to 24 hr after discontinuation of treatment. This makes terlipressin an excellent therapeutic agent for the early phase of bleeding, when buying time to organize definitive forms of treatment is essential.

To our surprise, definitive control of bleeding could be obtained only in about 46% of patients treated by a combination of DDAVP and terlipressin. Because spontaneous cessation of bleeding may be expected to occur in up to 50% of patients (18), these results suggest that the addition of DDAVP reversed the favorable effect of terlipressin in achieving complete control of bleeding, although it did not affect transfusion requirement or survival.

Because the trial was designed on the basis of a two-sided test, from a purely statistical point of view, we should have continued the study until a significant difference in either direction was observed or the programmed number of patients was enrolled. However, we decided to terminate the study after the interim analysis because we felt it ethically unjustifiable to continue to treat patients with DDAVP when our data indicated that DDAVP does not improve and may even worsen the efficacy of terlipressin.

We cannot rule out the possibility that DDAVP, given on a different schedule of administration, might be more effective. The schedule evaluated in this trial was chosen because the effects of DDAVP on hemostasis measurements are evident shortly after the administration of the drug and last for 4 to 6 hours (14). In principle, therefore, such effects could be most useful in two circumstances: at the beginning of terlipressin treatment, when improvement of hemostasis measurements might concur with the decrease of portal pressure induced by terlipressin in achieving control of the hemorrhage, and at the end of terlipressin treatment, when the return of portal pressure to baseline values might be responsible for the recurrence of hemorrhage. At this critical time, the improvement in hemostasis induced by DDAVP might decrease the risk of recurrence. We gave the second dose of DDAVP 2 hr after the last dose of terlipressin so that the maximum effect of DDAVP would overlap the decreasing effect of terlipressin. We did not consider giving DDAVP every 4 to 6 hr throughout terlipressin treatment because patients repeatedly treated with DDAVP at closely spaced intervals may become progressively unresponsive (19) and experience hyponatremia. Hence we decided to administer DDAVP twice, at the times when its effect could be most useful.

It is difficult to explain the deleterious effect of DDAVP. Because DDAVP increases the plasma levels of tissue-type plasminogen activator (20) and hyperfibrinolysis seems to increase the risk of gastrointestinal

hemorrhage in cirrhosis (21), one may speculate that DDAVP-induced hyperfibrinolysis would offset the beneficial effect of terlipressin. On the other hand, the effect of DDAVP on the tissue-type plasminogen activator is marked but very short-lasting. In other clinical settings, the net effect of DDAVP is positive for hemostasis, despite the increase of tissue-type plasminogen activator (19). Another possible explanation is that DDAVP competes with terlipressin for the V1 vasopressin receptor on the smooth muscle cells, decreasing the vasoconstrictor effect. However, this is less likely because the relative affinity of DDAVP and terlipressin for the V1 receptor is 1:2,000 to 3,000 (22). On the other hand, interaction between the two drugs may be a two-way phenomenon leading to decreases in both the hemostatic effects of DDAVP and the vasoactive action of terlipressin.

In conclusion, the addition of the hemostatic agent DDAVP to the vasoactive drug terlipressin in the treatment of acute variceal bleeding in cirrhotic patients does not improve and possibly worsens the efficacy of terlipressin.

In view of these results, more knowledge is needed about the changes in hemostasis and in splanchnic hemodynamics that occur in cirrhotic patients when DDAVP and terlipressin are simultaneously administered. At this point, no clinical recommendation about the use of DDAVP in conjunction with terlipressin to treat bleeding cirrhotic patients can be made.

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