

SCLEROTHERAPY WITH OR WITHOUT OCTREOTIDE FOR ACUTE VARICEAL BLEEDING

ISABELLE BESSON, M.D., PIERRE INGRAND, M.D., BRUNO PERSON, M.D., DOMINIQUE BOUTROUX, M.D., DENIS HERESBACH, M.D., PIERRE BERNARD, M.D., PATRICK HOCHAIN, M.D., JACQUES LARRICQ, M.D., ALAIN GOURLAOUEN, M.D., DIDIER RIBARD, M.D., NASSIM MOSTEFA KARA, M.D., JEAN-LOUIS LEGOUX, M.D., BERNARD PILLEGAND, M.D., MARIE-CLAUDE BECKER, M.D., JACQUES DI COSTANZO, M.D., JEAN-MICHEL METREAU, M.D., CHRISTINE SILVAIN, M.D., AND MICHEL BEAUCHANT, M.D.

Abstract *Background.* Sclerotherapy is considered the most effective way to stop bleeding from esophageal varices, but acute variceal bleeding is still associated with a high risk of rebleeding and death. We compared sclerotherapy alone with sclerotherapy and octreotide to control acute variceal bleeding and prevent early rebleeding in patients with cirrhosis.

Methods. In a double-blind, prospective trial, 199 patients with cirrhosis and acute variceal bleeding who underwent emergency sclerotherapy were randomly assigned to receive a continuous infusion of octreotide (25 μ g per hour) or placebo for five days. The primary outcome measure was survival without rebleeding five days after sclerotherapy.

Results. After five days, the proportion of patients who had survived without rebleeding was higher in the octreotide group (85 of 98 patients, or 87 percent) than in the placebo group (72 of 101, or 71 percent; 95 percent confidence interval for the difference, 4 to 27 percent; $P=0.009$). The mean number of units of blood transfused within the first 24 hours after sclerotherapy was lower in

the octreotide group (1.2 units; range, 0 to 7) than in the placebo group (2.0 units; range, 0 to 10; $P=0.006$). A logistic-regression analysis showed that the treatment assignment ($P=0.003$) and the number of blood units transfused before any other treatment was undertaken ($P=0.002$) were the only two variables independently associated with survival without rebleeding. After adjustment for base-line differences between the two groups, the odds ratio for treatment failure in the placebo group, as compared with the octreotide group, was 3.3 (95 percent confidence interval, 1.5 to 7.3). The mean (\pm SD) 15-day cumulative survival rate (estimated by the Kaplan-Meier method) was 88 ± 12 percent in both groups. Side effects were minor, and their incidence was similar in the two groups.

Conclusions. In patients with cirrhosis, the combination of sclerotherapy and octreotide is more effective than sclerotherapy alone in controlling acute variceal bleeding, but there is no difference between the overall mortality rates associated with the two approaches to treatment. (*N Engl J Med* 1995;333:555-60.)

ACUTE bleeding from esophageal varices is a major problem in patients with cirrhosis of the liver and is associated with a 30 to 50 percent risk of death.¹⁻³ Sclerotherapy is considered the most effective way to stop bleeding and is the main form of emergency treatment in most institutions.⁴ However, the success rate varies widely, partly because the definitions of success vary and partly because other methods, such as balloon tamponade and the administration of vasopressin, are used at the same time. Bleeding is controlled during the first five days in about 80 to 90 percent of patients,^{4,5} depending on the endoscopist's experience and the severity of liver disease. Serious side effects, such as bleeding ulcer and esophageal perforations, can occur in patients receiving multiple injections of a sclerosant. As a result, sclerotherapy has no influence on the mortality rate at six weeks.³

Octreotide, a synthetic somatostatin analogue, has a much longer half-life (one to two hours) than native somatostatin (one to two minutes) but has the same therapeutic properties. The drug reduces collateral splanchnic blood flow without causing adverse systemic effects.⁶ Like native somatostatin, octreotide is at least as effective as balloon tamponade⁷ and vasopressin deriva-

tives⁸⁻¹⁰ in controlling variceal bleeding. Somatostatin and octreotide are the only vasoactive drugs known to be as effective as emergency sclerotherapy.^{11,12} The combination of somatostatin and balloon tamponade does not appear to be more effective than either treatment used alone.¹³ There are few clinical data, however, on the effectiveness of sclerotherapy combined with vasoactive drugs.¹⁴

In a prospective, double-blind, randomized trial, we compared sclerotherapy alone with a combination of sclerotherapy and octreotide to control acute variceal bleeding and prevent early rebleeding in patients with cirrhosis.

METHODS

Enrollment of Patients

All adults with hematemesis or melena (or both) admitted to the liver units of 15 French medical centers underwent endoscopy as soon as they had been resuscitated. Patients were enrolled in the trial if they had active variceal bleeding at endoscopy (spurting or oozing from esophageal or cardiac varices) or nonbleeding varices but evidence of blood with no other potential source of gastrointestinal bleeding and if less than 24 hours had elapsed between the occurrence of hematemesis or melena (or both) and the emergency endoscopy. Cirrhosis was documented on the basis of a liver biopsy performed during a previous admission or typical laboratory and clinical findings.

Patients were ineligible if they had during an earlier admission been randomly assigned to a treatment group in this trial; had had bleeding from esophageal varices within the previous 15 days, if sclerotherapy had been administered, or within the previous 8 days, if only balloon tamponade or vasoactive drugs had been used; had severe liver failure (defined as a hepatorenal syndrome or end-stage

From the Service d'Hépatogastroentérologie, Centre Hospitalier Universitaire de Poitiers, Poitiers, France. Address reprint requests to Dr. Beauchant at the Service d'Hépatogastroentérologie, B.P. 577, 86021 Poitiers, France.

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The centers and investigators participating in the study are listed in the Appendix.

cirrhosis); had received treatment with balloon tamponade or vasoactive drugs during the bleeding episode; had hepatocellular carcinoma or noncirrhotic portal hypertension; or were 80 years old or older.

The protocol was approved by the hospital ethics committee at Centre Hospitalier Universitaire de Poitiers, in keeping with French laws governing clinical research. Because the study was conducted under emergency conditions, written informed consent could be obtained from the patients only when they were in stable condition, which was generally after the start of the drug infusion; the relatives of patients with severe encephalopathy were asked to provide consent for enrollment. The ethics committee approved these exceptions to the requirement of prior written consent because of the emergency nature of the treatment.

Treatment

Patients who met the enrollment criteria underwent emergency sclerotherapy during the initial endoscopy. Two percent polidocanol solution was injected by the freehand technique, with a flexible needle injector inserted through the biopsy channel of the flexible endoscope. The injections, which were intravariceal or paravariceal or both, were begun at the esophagogastric junction and administered only at the most likely site of hemorrhage. The maximal volume of sclerosant injected was 20 ml. The number of injections was not recorded.

Randomization was carried out in blocks of four (i.e., the test substance was octreotide in two cases and placebo in the other two). Each hospital had a consecutively numbered series of sealed boxes corresponding to the assigned treatment (Sandoz Pharmaceuticals, Rueil Malmaison, France). Each box contained six identical ampules of octreotide or placebo, so that neither the physicians nor the patients were aware of the treatment. The code assigning patients to their treatment groups was kept by the statistician in charge of the analysis. Immediately after undergoing sclerotherapy, the patients were consecutively assigned to receive an infusion of octreotide or placebo for 120 hours (five days) at a rate of 25 μg per hour administered through a syringe pump. Each ampule of placebo or octreotide (500 μg) was diluted to 50 ml with 0.9 percent saline. Conventional supportive therapy, including the administration of intravenous fluids, vitamins, and lactulose, was given as indicated clinically. After the end of the drug infusion (from day 5 to day 7), a second sclerotherapy session was allowed, and the presence and severity of esophageal ulcers (grade 0, absent; grade 1, moderate; or grade 2, large or necrotic) were recorded. Blood pressure, pulse, hematocrit, transfusion requirements, and adverse effects of octreotide or placebo were monitored throughout the treatment period.

The primary outcome measure was survival without rebleeding five days (120 hours) after sclerotherapy, which was considered to indicate the control of acute variceal bleeding without rebleeding or death. Death, regardless of the precise cause, was considered to be related to variceal bleeding.¹⁵ A secondary end point was the amount of blood transfused during the first 24 hours after sclerotherapy. Variceal bleeding was considered to have been controlled if the following criteria were met¹⁶: stable blood pressure (no reduction in systolic pressure exceeding 20 mm Hg, once the blood pressure had stabilized); a stable hemoglobin concentration (>9 g per deciliter), measured twice daily; and a hematocrit above 30 percent (measured hourly during the first 12 hours and every 2 to 6 hours thereafter, depending on the patient's hemodynamic status), with a transfusion requirement of no more than two units in a 2-hour period and fewer than four units within the first 4 hours after sclerotherapy.

Major adverse events necessitating the termination of treatment were recorded, as well as minor side effects (abdominal pain, nausea, headache, diarrhea, and hyperglycemia) and the occurrence of a hepatorenal syndrome or severe encephalopathy. All patients were monitored in the hospital and as outpatients for a minimum of 15 days after the first sclerotherapy session.

Statistical Analysis

Analyses were performed on an intention-to-treat basis and included all patients who underwent randomization. The two treatment

groups were compared on the basis of the primary outcome measure with the use of Fisher's exact test, and the analysis was stratified according to the Child-Pugh class¹⁷ and the presence or absence of active bleeding at the time of the initial endoscopy, with the use of the Mantel-Haenszel test. The Mann-Whitney test was used to compare transfusion requirements in the two groups. Prognostic variables were tested against the primary outcome measure in a backward logistic-regression analysis. The odds ratio for treatment failure in the placebo group as compared with the octreotide group was then calculated. Kaplan-Meier analyses were used to calculate overall survival and survival without rebleeding at 15 days. All P values were two-tailed; P values of less than 0.05 were considered to indicate statistical significance.¹⁸ Analyses were performed with SAS software.¹⁹

RESULTS

Patients

From November 1992 to September 1994, 360 consecutive patients with variceal bleeding were evaluated at the 15 centers participating in the trial. Five centers joined the trial in May 1993. One center withdrew four months later, after four patients had been evaluated. Two of these patients did not meet the inclusion criteria or declined to participate; the other two were included in the analysis. A total of 159 other patients were excluded from the trial for the following reasons: previous treatment, such as balloon tamponade or vasoactive drugs (78 patients); an initial endoscopy without sclerotherapy (25); hepatocellular carcinoma (23); refusal to participate (16); death before sclerotherapy (9); and severe liver disease (8).

Of the 199 patients who underwent emergency sclerotherapy and were enrolled in the study (2 to 27 patients per center), 98 received octreotide and 101 received placebo. The two groups had similar baseline characteristics (Table 1), with the exception of the Child-Pugh class, the value for total bilirubin, and the prothrombin time, which were all higher in the placebo group. More patients in the placebo group than in the octreotide group had received propranolol during the month before the index bleeding. The interval between clinical signs of bleeding and the initial endoscopy with emergency sclerotherapy was similar in the two groups, as were the percentage of patients with active bleeding at the initial endoscopy and the total dose of sclerosant injected (mean volume, 17.0 ml in the octreotide group and 16.9 ml in the placebo group). One hundred ten patients had inactive bleeding at the initial endoscopy: 24 patients in the octreotide group and 21 in the placebo group had clots on varices; 32 patients in the octreotide group and 33 in the placebo group had no other potential cause of bleeding.

End Points

After five days, the proportion of patients who had survived without rebleeding was significantly higher in the octreotide group (85 of 98 patients, or 87 percent) than in the placebo group (72 of 101, or 71 percent; $P=0.009$ by Fisher's exact test; 95 percent confidence interval for the difference, 4.1 to 27.2 percent) (Table 2). Similarly, the rate of survival without rebleeding

Table 1. Base-Line Characteristics of 199 Patients with Acute Variceal Bleeding Treated with Sclerotherapy and Octreotide or Placebo.*

| CHARACTERISTIC | OCTREOTIDE (N = 98) | PLACEBO (N = 101) |
|--|---------------------|-------------------|
| Age (yr) | | |
| Mean | 56 | 56 |
| Range | 33–78 | 28–79 |
| Sex (M/F) | 72/26 | 80/21 |
| Alcoholic cirrhosis (no. of patients)† | 89 | 93 |
| Child–Pugh class (no. of patients)‡ | | |
| A | 26 | 17 |
| B | 46 | 37 |
| C | 26 | 47 |
| Active variceal bleeding (no. of patients) | 42 | 47 |
| Cardial variceal bleeding (no. of patients) | 20 | 20 |
| Encephalopathy (no. of patients) | | |
| Absent | 77 | 77 |
| Moderate | 18 | 19 |
| Severe | 3 | 5 |
| Bilirubin (mg/dl)§ | 2.3±1.7 | 3.5±3.7 |
| Albumin (g/dl) | 3.1±0.5 | 2.9±0.6 |
| Creatinine (mg/dl) | 1.0±0.4 | 1.0±0.5 |
| Prothrombin time (%)¶ | 55±15 | 51±13 |
| Hemoglobin (g/dl) | 8.9±2.2 | 8.4±2.4 |
| Previous variceal bleeding (no. of patients) | 45 | 48 |
| Previous elective sclerotherapy (no. of patients) | 21 | 23 |
| Interval between start of bleeding and enrollment (hr) | 12.0±6.5 | 11.5±7.2 |
| Blood transfused before enrollment (no. of units) | | |
| Mean | 1.5 | 1.4 |
| Median | 1 | 0 |
| Range | 0–8 | 0–8 |
| Previous propranolol therapy (no. of patients) | 14 | 28 |

*All the variables, except previous sclerotherapy, were used in a logistic-regression analysis. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4. Plus-minus values are means ±SD.

†In the octreotide group, cirrhosis was diagnosed by biopsy in 68 patients and by clinical and laboratory criteria in 32. In the placebo group it was diagnosed by biopsy in 55 and by clinical and laboratory criteria in 46.

‡Class A denotes good hepatic function, class B intermediate hepatic function, and class C poor hepatic function. P=0.03 for the comparison between groups by Fisher's exact test.

§P=0.03 for the comparison between groups by the Mann–Whitney test.

¶Expressed as a percentage of the control value. P=0.04 for the comparison between groups by the Mann–Whitney test.

was higher in the octreotide group than in the placebo group when the data were analyzed according to the Child–Pugh class of hepatic function (class A [good function], 96 percent vs. 82 percent; class B [intermediate function], 83 percent vs. 73 percent; and class C [poor function], 85 percent vs. 66 percent; P=0.02 by the adjusted Mantel–Haenszel test). The difference remained significant after simultaneous adjustment for the Child–Pugh class of hepatic function, the presence or absence of active bleeding at initial endoscopy, and previous treatment with propranolol or the absence of such treatment (P=0.036 by the Mantel–Haenszel test).

The mean number of units of blood transfused within the first 24 hours after sclerotherapy was significantly lower in the octreotide group (mean, 1.2 units; median, 1; range, 0 to 7) than in the placebo group (mean,

2.0 units; median, 2; range, 0 to 10; P=0.006 by the Mann–Whitney test). Among the patients who survived with no rebleeding at five days, 37 of 85 (44 percent) in the octreotide group did not require further blood transfusions after sclerotherapy, as compared with 20 of 72 (28 percent) in the placebo group (P=0.03 by the Mann–Whitney test). Between 24 and 120 hours after sclerotherapy, the transfusion requirements were similar in the two groups: a mean of 0.4 unit (median, 0; range, 0 to 5) in the octreotide group and 0.8 unit (median, 0; range, 0 to 6) in the placebo group.

A logistic-regression analysis (incorporating all the characteristics in Table 1) indicated that the factors independently associated with survival without rebleeding after five days were the treatment assignment (P=0.003) and the number of units of blood transfused before the administration of the assigned treatment (P=0.002). The latter variable was negatively correlated with survival without rebleeding and positively correlated with the Child–Pugh class of hepatic function and the serum creatinine level. After adjustment for base-line differences between the two groups, the odds ratio for treatment failure in the placebo group, as compared with the octreotide group, was 3.3 (95 percent confidence interval, 1.5 to 7.3).

Survival

During the five-day study period, 11 patients in the octreotide group and 25 patients in the placebo group had uncontrolled bleeding or rebleeding (Table 2); they were subsequently treated with further sclerotherapy, ligation, balloon tamponade, or vasoactive drugs. The selection of additional treatment varied from one center to another. Five of the 11 patients in the octreotide

Table 2. Outcomes in the Octreotide and Placebo Groups.

| OUTCOME | OCTREOTIDE (N = 98) | PLACEBO (N = 101) |
|---|---------------------|-------------------|
| Survival without rebleeding at 5 days — no./total no. (%) | 85/98 (87)* | 72/101 (71) |
| Child–Pugh class — no./total no. (%)† | | |
| A | 25/26 (96) | 14/17 (82) |
| B | 38/46 (83) | 27/37 (73) |
| C | 22/26 (85) | 31/47 (66) |
| Uncontrolled bleeding, 0 to 24 hr — no. of patients | 3 | 15 |
| Rebleeding, 25 to 120 hr — no. of patients | 8 | 10 |
| Mean units of blood transfused — no. (median, range) | | |
| 0 to 24 hr | 1.2 (1, 0–7)‡ | 2.0 (2, 0–10) |
| 25 to 120 hr | 0.4 (0, 0–5) | 0.8 (0, 0–6) |
| Death at 5 days — no./total no. (%) | 7/98 (7) § | 10/101 (10) |
| With bleeding | 5 | 6 |
| Without bleeding | 2 | 4 |
| Rebleeding, days 5 to 15 — no. of patients¶ | 3 | 4 |
| Death, days 5 to 15 — no. of patients | 5 | 2 |

*P=0.009 by Fisher's exact test; P=0.02 by the Mantel–Haenszel test, after adjustment for the Child–Pugh class.

†The Child–Pugh classes are defined in Table 1.

‡P=0.006 by the Mann–Whitney test.

§P=0.49 by the log-rank test.

¶Among those who were alive without bleeding at five days.

group and 6 of the 25 in the placebo group died while the bleeding was uncontrolled.

A total of seven patients in the octreotide group died during the five-day study period: five with uncontrolled bleeding and two with severe encephalopathy. Ten patients in the placebo group died: six with uncontrolled bleeding, two with metabolic acidosis, and two with severe encephalopathy. The numbers of deaths in the two groups, according to the Child–Pugh class of hepatic function, were as follows: class A, one death in the octreotide group and none in the placebo group; class B, three deaths in each group; and class C, three deaths in the octreotide group and seven in the placebo group.

Over a 15-day period, treatment failed (i.e., bleeding was not controlled or death occurred) in 13 patients in the octreotide group, 2 of whom died even though the bleeding was controlled (Table 2). Treatment failed in 29 patients in the placebo group, including 4 in whom bleeding had been controlled. The cumulative rates of survival without rebleeding at 15 days are shown in Figure 1. The mean (\pm SD) rate of overall survival at 15 days was 88 ± 12 percent in both groups ($P = 0.95$ by the log-rank test) (Fig. 2). At 15 days, 12 patients in each group had died. Five of the deaths in the octreotide group and four of those in the placebo group were unrelated to bleeding.

Complications

All side effects in both groups were minor (Table 3) and did not require termination of the drug infusion.

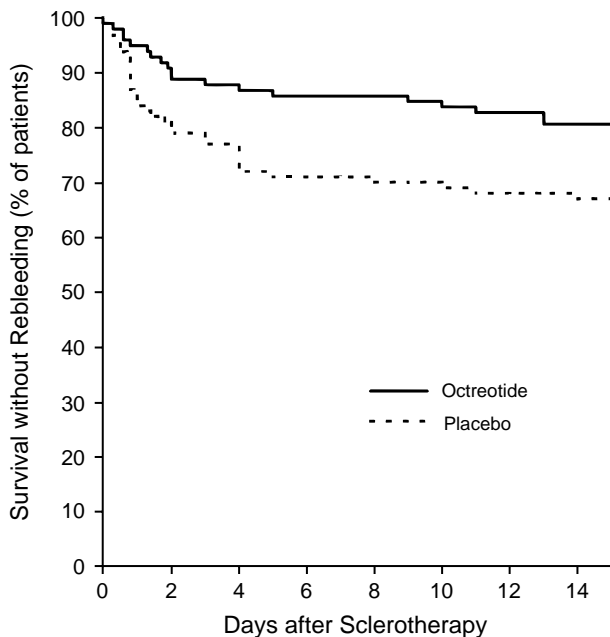


Figure 1. Kaplan–Meier Estimates of Survival without Rebleeding after Sclerotherapy in the Octreotide and Placebo Groups. The analysis was done on an intention-to-treat basis, and death was considered to be related to variceal bleeding regardless of the precise cause ($P = 0.02$ by the adjusted Mantel–Haenszel test).

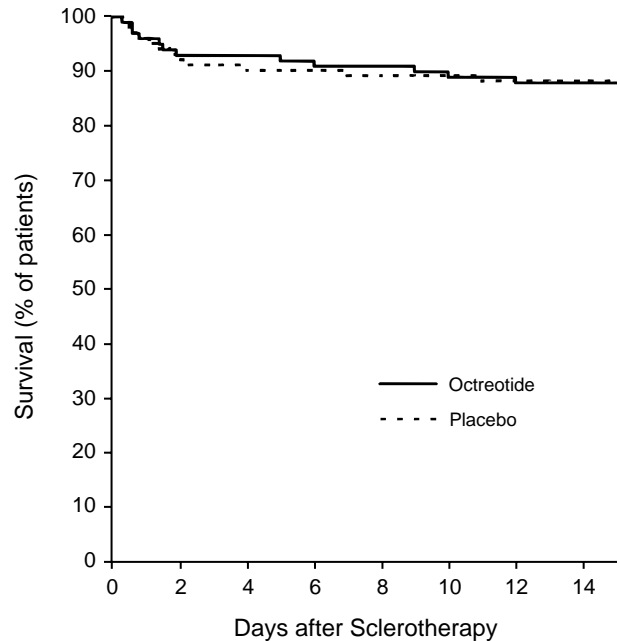


Figure 2. Kaplan–Meier Estimates of Survival after Sclerotherapy in the Octreotide and Placebo Groups ($P = 0.95$ by the Log-Rank Test).

The number of patients with hyperglycemia was higher in the octreotide group than in the placebo group (23 vs. 13; $P = 0.065$ by Fisher's exact test). A total of 134 patients (65 in the octreotide group and 69 in the placebo group) underwent a second sclerotherapy session between days 5 and 7.

The frequency and severity of esophageal ulcers were similar in the two groups: 37 patients in the octreotide group and 39 in the placebo group did not have ulcers, 22 in the octreotide group and 23 in the placebo group had grade 1 ulcers, and 6 in the octreotide group and 7 in the placebo group had grade 2 ulcers.

Severe encephalopathy and death occurred during the drug infusion in three patients in the octreotide group and two in the placebo group. After the five-day study period, a severe hepatorenal syndrome and death occurred in one patient in the octreotide group and two in the placebo group.

DISCUSSION

In a placebo-controlled trial with 199 patients, we evaluated the efficacy of treatment with octreotide after emergency sclerotherapy for the control of acute variceal bleeding in a group of patients, most of whom had cirrhosis because of alcohol use. As compared with placebo, octreotide was associated with a significantly higher rate of survival without rebleeding at five days, although the overall mortality rate was unaffected. Octreotide was also associated with a reduction in transfusion requirements, and the drug caused no major side effects. The difference in outcomes was not affected by the Child–Pugh class of hepatic function.

Table 3. Adverse Effects at Five Days.

| ADVERSE EFFECT | OCTREOTIDE | PLACEBO |
|---|-----------------|-----------|
| | (N = 98) | (N = 101) |
| | no. of patients | |
| Headache | 2 | 6 |
| Nausea | 0 | 3 |
| Diarrhea | 5 | 0 |
| Abdominal pain | 0 | 4 |
| Hyperglycemia* | 23† | 13 |
| Severe encephalopathy | 3 | 2 |
| Renal failure | 0 | 0 |
| Spontaneous bacterial peritonitis or septic shock | 1‡ | 1§ |
| Metabolic acidosis | 0 | 2 |
| Disseminated intravascular coagulopathy | 0 | 2¶ |
| Death related to adverse effect | 2 | 6 |

*Hyperglycemia was defined as a blood glucose concentration greater than 120 mg per deciliter (6.7 mmol per liter).

†P = 0.065 by Fisher's exact test.

‡The patient had associated metabolic acidosis.

§The patient had associated severe encephalopathy.

¶One patient had associated metabolic acidosis. Both patients died, one with uncontrolled bleeding.

In our study, emergency endoscopy was performed as soon as the patients had been resuscitated. The patients could not be stratified according to the Child-Pugh score at this time, since not all the laboratory data used to calculate the score were available. Therefore, the two patient groups differed according to the Child-Pugh score. Shields et al.²⁰ and Sung et al.¹² found that Child-Pugh class C hepatic function was independently associated with early rebleeding after sclerotherapy or treatment with somatostatin or octreotide, although Barsoum et al.,²¹ who compared sclerotherapy with balloon tamponade, did not report an association with class C function. Planas et al.¹¹ compared the efficacy of somatostatin with that of sclerotherapy and stratified patients according to the presence or absence of active bleeding and clinical signs of severe liver disease, since the Child-Pugh score could not be determined in the emergency setting. No factors predictive of treatment failure during the first 48 hours were identified. Rebleeding between day 2 and day 7 was independently associated with severe liver disease, the presence of both hypovolemia before randomization and active bleeding at diagnostic endoscopy, and nonalcoholic causes of cirrhosis. The definitions of acute bleeding and early rebleeding have differed widely among these other studies. In our study, aside from the treatment-group assignment, the only factor independently associated with survival without rebleeding at five days was the number of blood units transfused before the initial endoscopy. The number of units transfused was also correlated with the severity of liver disease.

The efficacy of emergency sclerotherapy depends mainly on the endoscopist's experience, the number of sessions, and whether this approach is used alone or with other approaches, such as balloon tamponade or the

administration of vasopressin. The rate of controlled bleeding in our placebo group was similar to that reported in randomized studies involving a single sclerotherapy session. Planas et al.¹¹ controlled bleeding for seven days in 24 of 35 patients (69 percent), and Shields et al.²⁰ controlled bleeding for five days in 34 of 41 patients (83 percent). Burroughs et al.⁵ reported a 62 percent success rate (control of bleeding in 31 of 50 patients) five days after sclerotherapy in a group of patients with uncontrolled bleeding after transfusions and the administration of vasoactive drugs. Burroughs et al.⁵ also reviewed prospective and randomized series and found that the success rate for sclerotherapy ranged from 50 to 87 percent. These differences emphasize the importance of conducting large, double-blind trials.

As in our previous trial,¹⁰ the infusion of octreotide did not appear to have severe adverse effects. The drug theoretically reduces the glomerular filtration rate, but evidence of this effect remains controversial.²² Dudley suggested that octreotide may increase the intestinal transit time and induce the onset of encephalopathy.²³ In our study, however, the incidence of severe encephalopathy and the incidence of renal failure were similar in the two treatment groups.

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APPENDIX

The following centers and investigators participated in the study: *Centre Hospitalier Universitaire, Poitiers* — M. Beauchant, I. Besson, P. Ingrand, C. Silvain; *Centre Hospitalier Universitaire, Angers* — B. Person, P. Calès; *Centre Hospitalier, Saint Brieuc* — D. Boutroux, O. Nouel; *Centre Hospitalier Universitaire, Rennes* — D. Heresbach, J.F. Bretagne; *Centre Hospitalier Universitaire, Bordeaux* — P. Bernard, A. Quinton; *Centre Hospitalier Universitaire, Rouen* — P. Hochain, R. Colin; *Centre Hospitalier Universitaire, Strasbourg* — J. Larricq, M. Doffoel; *Centre Hospitalier Universitaire, Brest* — A. Gourlaouen, H. Gouerou; *Centre Hospitalier Universitaire, Nîmes* — D. Ribard, J.F. Balmes; *Centre Hospitalier Universitaire, Paris-Saint Antoine* — N.M. Kara, C. Florent; *Centre Hospitalier Régional, Orléans* — J.L. Legoux; *Centre Hospitalier Universitaire, Limoges* — B. Pillegand; *Centre Hospitalier Universitaire, Besançon* — M.-C. Becker, J.P. Miquet; *Centre Hospitalier Universitaire, Marseilles-Sainte Marguerite* — J. Di Costanzo, J. Sahel; and *Centre Hospitalier Universitaire, Créteil-Henri Mondor* — J.-M. Metreau, D. Dhumeaux.

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