

NADOLOL PLUS ISOSORBIDE MONONITRATE COMPARED WITH SCLEROTHERAPY FOR THE PREVENTION OF VARICEAL REBLEEDING

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Abstract *Background.* Patients who have bleeding from esophageal varices are at high risk for rebleeding and death. We compared the efficacy and safety of endoscopic sclerotherapy with the efficacy and safety of nadolol plus isosorbide mononitrate for the prevention of variceal rebleeding.

Methods. Eighty-six hospitalized patients with cirrhosis and bleeding from esophageal varices diagnosed by endoscopy were randomly assigned to treatment with repeated sclerotherapy (43 patients) or nadolol plus isosorbide-5-mononitrate (43 patients). The primary outcomes were rebleeding, death, and complications. The hepatic venous pressure gradient was measured at base line and after three months.

Results. Base-line data were similar in the two groups, and the median follow-up was 18 months in both. Eleven patients in the medication group and 23 in the sclerotherapy group had rebleeding. The actuarial probability of remaining free of rebleeding was higher in the medi-

cation group for all episodes related to portal hypertension ($P=0.001$) and variceal rebleeding ($P=0.002$). Four patients in the medication group and nine in the sclerotherapy group died ($P=0.07$ for the difference in the actuarial probability of survival). Seven patients in the medication group and 16 in the sclerotherapy group had treatment-related complications ($P=0.03$). Thirty-one patients in the medication group underwent two hemodynamic studies; 1 of the 13 patients with more than a 20 percent decrease in the hepatic venous pressure gradient had rebleeding, as compared with 8 of the 18 with smaller decreases in the pressure gradient ($P=0.04$ for the actuarial probability of rebleeding at two years).

Conclusions. As compared with sclerotherapy, nadolol plus isosorbide mononitrate significantly decreased the risk of rebleeding from esophageal varices. (N Engl J Med 1996;334:1624-9.)

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AFTER the initial control of a hemorrhage from esophageal varices, patients are at high risk for further bleeding and death.^{1,2} Therapy to prevent rebleeding is essential. Endoscopic sclerotherapy is widely used for this purpose. Meta-analyses of data from controlled trials have confirmed that rates of rebleeding are decreased and overall survival is improved by sclerotherapy.^{3,4} Several studies have compared sclerotherapy with beta-blockers for the prevention of rebleeding.⁵⁻¹¹ A meta-analysis of these studies showed that sclerotherapy was more effective for the prevention of rebleeding, but there was no difference in survival between the two therapies.⁴ Sclerotherapy is still associated with a rebleeding rate as high as 50 percent, however, and complications such as fever and esophageal ulceration or stricture occur in up to 40 percent of patients, with treatment-related deaths in 1 to 2 percent.¹²

Recent hemodynamic studies have shown that isosorbide mononitrate combined with propranolol results in a greater reduction in portal pressure than that achieved with propranolol alone¹³ and is also effective in patients who do not have a response to therapy with propranolol alone.¹⁴ We compared the efficacy and safety of endoscopic sclerotherapy with the efficacy and safety of nadolol plus isosorbide mononitrate for the prevention of variceal rebleeding. Nadolol was used instead of propranolol because it is not metabo-

lized by the liver and needs to be administered only once a day.¹⁵⁻¹⁷

METHODS

Selection of Patients

From August 1991 to January 1994, 765 patients were admitted to our hospital because of upper gastrointestinal bleeding. Of these patients, 121 met the following eligibility criteria: cirrhosis, emergency endoscopy performed within the first four hours after admission, and endoscopic evidence of a hemorrhage from esophageal varices. The diagnosis of cirrhosis was verified by clinical, biochemical, and echographic findings.

Thirty-five of the 121 patients were excluded for the following reasons: age under 18 years (2 patients), a Child-Pugh score higher than 12 points (11), advanced hepatocellular carcinoma (3), lung cancer (1), previous sclerotherapy (8), the failure of medical therapy to control the index bleeding (7), and refusal to participate in the study (3).

Randomization and Treatment

On the fifth hospital day, 86 patients were randomly assigned to one of two treatment groups with the use of opaque sealed envelopes that contained the treatment assignments, which were derived from computer-generated random numbers. Randomization was stratified according to the severity of liver failure, as assessed by the Child-Pugh classification (class A and B or class C), and the presence or absence of a history of variceal bleeding. Written informed consent was obtained from all the patients or their next of kin, and the trial was approved by the ethics committee of our hospital.

In the medication group, continuous pharmacologic therapy was started immediately after randomization. Nadolol was given orally at an initial dose of 80 mg once daily. The dose was subsequently adjusted over a period of five days until the resting heart rate had been reduced by 25 percent or was 55 beats per minute. Oral isosorbide mononitrate was started immediately after the dose of nadolol had been adjusted. The dose was increased progressively up to a dose of 40 mg twice a day over a period of one week, unless side effects appeared. Compliance was assessed at each follow-up visit by careful questioning of the patient and his or her relatives.

In the sclerotherapy group, sclerotherapy was performed by inject-

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Table 1. Clinical Features, Endoscopic Findings, and Serum Biochemical Values in Patients with Esophageal Varices Treated with Nadolol plus Isosorbide Mononitrate or Sclerotherapy.*

VARIABLE	MEDICATION GROUP (N = 43)	SCLEROTHERAPY GROUP (N = 43)
Base line		
Age — yr	58 ± 11	60 ± 12
Men/women — no. of patients	29/14	29/14
Alcoholic cirrhosis — no. of patients (%)	25 (58)	24 (56)
Viral cirrhosis — no. of patients (%)	13 (30)	17 (40)
Child–Pugh class — no. of patients†		
A	9	11
B	27	22
C	7	10
Previous bleeding — no. of patients (%)	5 (12)	5 (12)
Active hemorrhage — no. of patients (%)	16 (37)	18 (42)
Treatment of index episode — no. of patients (%)		
Sclerotherapy	8 (19)	11 (26)
Octreotide	17 (40)	12 (28)
Sclerotherapy plus octreotide	17 (40)	18 (42)
Balloon tamponade‡	1 (2)	2 (5)
Transfusions during index episode (units of packed red cells)		
Mean	2.3	2.3
Median	2	2
Range	0–7	0–8
Ascites — no. of patients (%)	17 (40)	22 (51)
Encephalopathy — no. of patients (%)	8 (19)	7 (16)
Variceal grade — no. of patients§		
1	3	2
2	30	31
3	10	10
Biochemical values¶		
Bilirubin — mg/dl	2.6 ± 2.8	2.5 ± 2.3
Albumin — g/liter	31 ± 6	30 ± 5
Prothrombin activity — %	67 ± 17	68 ± 17
Creatinine — mg/dl	1.0 ± 0.4	0.9 ± 0.2
Follow-up		
Abstinence from alcohol — no. of patients	23	19
Hepatocellular carcinoma — no. of patients (%)	3 (7)	6 (14)
Liver transplantation — no. of patients (%)	3 (7)	2 (5)
Duration of follow-up — mo		
Mean	19	18
Median	18	18
Range**	4–36	1–36
Loss to follow-up — no. of patients (%)‡‡	1 (2)	1 (2)

*Plus–minus values are means ± SD. No differences between the groups were statistically significant.

†The Child–Pugh class was determined on the basis of data collected at randomization. Class A denotes good hepatic function (a score of 5 or 6), class B intermediate function (a score of 7 to 9), and class C poor function (a score of 10 to 12).

‡Balloon tamponade was performed in association with octreotide therapy and sclerotherapy.

§Grade 1 denotes varices that were flattened by insufflation, grade 2 varices that were not flattened by insufflation and were separated by areas of normal mucosa, and grade 3 confluent varices that were not flattened by insufflation.

¶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.

||Five patients were referred for orthotopic liver transplantation between the 10th and the 25th month of follow-up.

**Three patients in the sclerotherapy group died after only one month of follow-up.

‡‡One patient in the medication group was lost to follow-up after six months, and one patient in the sclerotherapy group was lost to follow-up after nine months.

ing 5 percent ethanolamine into all esophageal varices at different levels within the lower 4 cm of the esophagus, up to a total dose of 10 to 20 ml. Sclerotherapy sessions were carried out on days 0 (the day of randomization), 4, 10, and 30, and then monthly until the varices were eradicated. After eradication, follow-up endoscopic studies (with further sclerotherapy sessions if the varices reappeared) were performed at three months and subsequently every six months.

Follow-up and End Points

The study continued until seven months after the enrollment of the last patient. The primary end points were rebleeding, complications, and death.

Rebleeding was defined as any episode of hematemesis or melena

(or both) occurring during follow-up and was evaluated by emergency endoscopy. In both groups, the index hemorrhage, as well as rebleeding, was treated with octreotide or emergency sclerotherapy, or both. We calculated the rebleeding index for each patient by dividing the months of follow-up by the number of rebleeding episodes plus 1, as suggested in a consensus workshop.¹⁸ This index reflects the time free of rebleeding during follow-up. Treatment failure was defined as the occurrence of two or more rebleeding episodes that required the transfusion of at least 2 units of red cells or continued hemorrhage despite medical treatment, requiring the transfusion of 4 or more units of red cells. For patients in whom the study treatment failed, decisions about alternative treatment were made individually.

Hemodynamic Studies

Hemodynamic studies were performed before randomization and again three to four months after the start of the drug treatment or after the completion of the sclerotherapy sessions. After an overnight fast, a venous catheter with an introducer sheath was placed in the right femoral vein by the Seldinger technique and used to advance, under fluoroscopic guidance, a 7-French balloon-tipped catheter (Meditech) into the right main hepatic vein and a Swan–Ganz catheter (Abbott Laboratories) into the pulmonary artery. Portal pressure was measured as the hepatic venous pressure gradient. Cardiopulmonary pressures and cardiac output were also measured. All measurements were performed in triplicate with the use of a previously calibrated strain-gauge transducer, with the midaxillary line as the zero reference point.

Statistical Analysis

In calculating the sample size, we assumed a 50 percent rebleeding rate in the sclerotherapy group.¹⁹ Forty-two patients were required in each treatment group to detect a difference of at least 30 percent, with alpha and beta values of 0.05 and 0.2, respectively.

The statistical analysis was performed according to an intention-to-treat strategy. Qualitative variables were compared with Fisher's exact test. Student's t-test was used to compare the mean values for continuous variables, and the Wilcoxon rank-sum test was used for skewed or ordinal data.²⁰ Actuarial probabilities were calculated by the Kaplan–Meier method and compared with the log-rank test. Data were censored at the time of death

or at the last visit. The Cox proportional-hazards model was used to identify the subgroup of variables that best explained the differences in survival and rebleeding rates.²¹ All P values were two-tailed, and values of less than 0.05 were considered to indicate statistical significance.²² Calculations were performed with the BMDP statistical package.

RESULTS

Forty-three patients were randomly assigned to each treatment group. Base-line data were similar in the two groups, and the median follow-up in both groups was 18 months (Tables 1 and 2). Three patients in the med-

Table 2. Changes in Hemodynamic Variables, the Child–Pugh Score, and Plasma Urea and Creatinine Levels.

VARIABLE	MEDICATION GROUP		SCLEROTHERAPY GROUP	
	BASE LINE	3 MONTHS	BASE LINE	3 MONTHS
			<i>mean ±SD</i>	
Wedge hepatic venous pressure (mm Hg)	26.7±4.3	22.3±4.1*	24.8±6.4	26.3±5.5†
Free hepatic venous pressure (mm Hg)	8.9±3.5	8.3±2.6	8.0±4.1	8.8±2.7
Hepatic venous pressure gradient (mm Hg)	17.7±3.4	13.9±3.8*	16.8±4.3	17.4±5.1†
Cardiac output (liters/min)	7.4±1.8	5.4±1.6*	7.2±1.6	6.9±1.3†
Mean arterial pressure (mm Hg)	84.7±8.3	79.3±10.4*	85.1±12.4	82.6±9.3
Heart rate (beats/min)	76.6±12.0	58.7±4.9*	79.0±13.3	73.9±11.4†‡
Pulmonary wedge pressure (mm Hg)	9.1±2.7	10.3±3.9	8.5±3.1	10.7±3.6*
Right arterial pressure (mm Hg)	5.3±2.3	5.9±2.7	5.0±2.8	6.2±2.7§
Systemic vascular resistance (dyn·sec·cm ⁻⁵)	923±309	1081±215*	890±224	944±258
Child–Pugh score	7.8±1.6	6.2±1.2*	8.0±1.9	6.7±1.9*
Plasma urea (mg/dl)¶	48±21	35±14*	48±25	40±9*
Plasma creatinine (mg/dl)	1.0±0.4	1.0±0.3*	0.9±0.2	1.0±0.2*

*P<0.01 for the comparison with the base-line value.

†P<0.05 for the comparison with the value at three months in the medication group.

‡P<0.01 for the comparison with the base-line value in the sclerotherapy group.

§P<0.05 for the comparison with the base-line value.

¶To convert the values for urea to millimoles per liter, multiply by 0.167.

||To convert the values for creatinine to micromoles per liter, multiply by 88.4.

ication group had contraindications to the use of nadolol and received only isosorbide mononitrate. There were no patients with contraindications to isosorbide mononitrate or sclerotherapy. Only one patient (in the medication group) did not comply with the study protocol.

Rebleeding

Data on rebleeding are presented in Table 3 and Figure 1. The likelihood of rebleeding was significantly lower in the medication group than in the sclerotherapy group ($P=0.001$) (Fig. 1). Similarly, the actuarial probability of remaining free of rebleeding at two years was higher in the medication group than in the sclerotherapy group when the data were analyzed according to the Child–Pugh class: class A, 67 percent versus 48 percent; class B, 63 percent versus 49 percent; and class C, 60 percent versus 43 percent ($P=0.002$).

Esophageal varices were the most frequent site of rebleeding (Table 3). The actuarial probability of remaining free of variceal rebleeding was also higher in the medication group than in the sclerotherapy group at six months (86 percent vs. 56 percent) and at two years (75 percent vs. 45 percent; $P=0.002$ for both comparisons). In the Cox regression analysis, the treatment assigned was an independent predictor of rebleeding ($P=0.004$), as was the hepatic venous pressure gradient in the third month of follow-up ($P=0.04$).

The likelihood of treatment failure at two years was significantly lower in the medication group (10 percent) than in the sclerotherapy group (54 percent, $P<0.001$). Treatment failed in three patients in the medication group: two patients subsequently received portacaval shunts, and one, who had end-stage liver disease, received no further treatment. In the sclerotherapy group, treatment failed in 16 patients: 7 were subsequently

treated with nadolol and isosorbide mononitrate, 3 received portacaval shunts, 2 received transjugular intrahepatic portosystemic shunts, and the remaining 4 received no other treatment.

Survival

The actuarial probability of survival was higher in the medication group than in the sclerotherapy group, although the difference was not significant ($P=0.07$) (Fig. 2). Nine patients in the sclerotherapy group and four in the medication group died. Seven patients (five in the sclerotherapy group and two in the medication group) died of liver failure. Death was related to rebleeding in two patients (both in the sclerotherapy group) and to hepatocellular carcinoma in three (two in the sclerotherapy group and one in the medication group). One patient in the medication group died of a stroke.

Cox proportional-hazards regression analysis showed that the following variables were independent predictors of mortality: the Child–Pugh score in the third month of follow-up ($P<0.001$), the hepatic venous pressure gradient in the third month of follow-up ($P=0.03$), and rebleeding ($P=0.06$).

Complications and Subsidiary Outcomes

Seven patients in the medication group had treatment-related complications, as compared with 16 in the sclerotherapy group ($P=0.03$). In the sclerotherapy group, seven patients had bleeding esophageal ulcers, two had aspiration pneumonia, two had esophageal strictures, two had pleural effusions, and three had septic complications. In the medication group, three patients had resting heart rates of less than 50 beats per minute, two had weakness and dyspnea, one had bronchospasm, and one had impotence. Nadolol had to be

Table 3. Rebleeding in the Study Groups.*

VARIABLE	MEDICATION GROUP (N = 43)	SCLEROTHERAPY GROUP (N = 43)
Rebleeding (no. of patients)†	11	23
Site of rebleeding (no. of patients)		
Esophageal varices‡	9	22
Esophageal ulcer§	0	5
Portal hypertensive gastropathy¶	0	4
Gastric varices	1	2
Undetermined	2	3
Other**	1	1
No. of rebleeding episodes	16	48
No. of rebleeding episodes per patient††	0.3±0.6	1.1±1.2
Rebleeding index‡‡	15.5±7.6	12.1±9.7
Transfusions (units)†††		
Mean	2.6	4.9
Median	2	4
Range	0–9	0–12
Treatment failure (no. of patients)§§	3	16
Hospital days¶¶	23±13	31±14
No. of hospital admissions not due to rebleeding	10	14

*Plus-minus values are means ±SD. The mean dose of nadolol was 110±70 mg per day, and the mean dose of isosorbide mononitrate was 70±18 mg per day. The mean number of sclerotherapy sessions performed was 5±1.6.

†P=0.001, by the log-rank test, for the comparison between the groups. In the medication group, one additional patient had rebleeding from a peptic ulcer. If this patient is included, the P value is 0.002.

‡P=0.002, by the log-rank test, for the comparison between the groups. In the medication group, 9 patients had 12 rebleeding episodes from esophageal varices. In the sclerotherapy group, 22 patients had 33 rebleeding episodes from esophageal varices.

§P=0.02, by the log-rank test, for the comparison between the groups.

¶P=0.03, by the log-rank test, for the comparison between the groups.

||Three patients had more than one potential bleeding site at endoscopy, and two patients (both in the sclerotherapy group) did not undergo endoscopy.

**One patient in the medication group had reflux esophagitis, and one patient in the sclerotherapy group had rectal varices.

††P<0.001 for the comparison between the groups.

‡‡The rebleeding index was calculated by dividing the months of follow-up by the number of rebleeding episodes plus 1. This index reflects the time free of rebleeding during follow-up. P=0.025 for the comparison between the groups.

§§P<0.001, by the log-rank test, for the comparison between the groups.

¶¶P=0.02 for the comparison between the groups.

discontinued in four of the patients (those with bradycardia or bronchospasm). None of the complications were fatal.

At the index endoscopy, four patients in each group had moderate portal hypertensive gastropathy. At the last endoscopy performed during follow-up, 6 patients in the medication group and 31 in the sclerotherapy group had moderate or severe portal hypertensive gastropathy (P<0.001).

Kidney function varied in similar fashion in the two groups, and laboratory values remained within the normal range (Table 2). During follow-up, ascites developed in 15 patients in the medication group (6 of whom had no history of ascites) and in 18 patients in the sclerotherapy group (9 of whom had no history of ascites).

Hemodynamic Measurements

Two hemodynamic studies were performed in 31 patients in each group; the second study could not be carried out in the remaining patients because of previous treatment failure or refusal of consent.

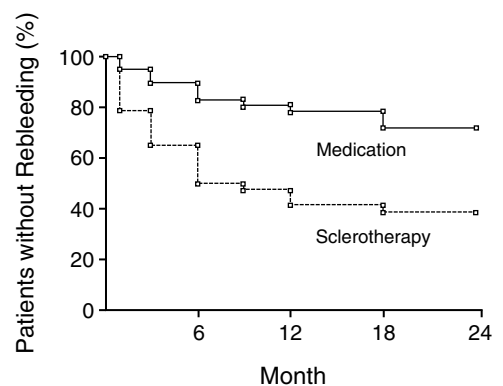
Continued drug therapy, but not sclerotherapy, sig-

nificantly reduced the hepatic venous pressure gradient (Table 2). The gradient decreased to less than 12 mm Hg in nine patients in the medication group and in two patients in the sclerotherapy group (P=0.04). The hepatic venous pressure gradient decreased by more than 20 percent from the base-line value in 13 patients in the medication group and in 4 in the sclerotherapy group (P=0.02). In two patients (one in each group), the gradient fell below 12 mm Hg, but the value was not more than 20 percent below the base-line value.

Bleeding did not recur in any of the patients who had a hepatic venous pressure gradient below 12 mm Hg. In the medication group, bleeding recurred in 1 of the 13 patients who had a decrease of more than 20 percent from the base-line value and in 8 of 18 with a 20 percent or smaller decrease; the actuarial probability of rebleeding at two years in these two groups was 33 and 47 percent, respectively (P=0.04). In the sclerotherapy group, bleeding recurred in none of the 4 patients with a decrease of more than 20 percent in the hepatic venous pressure gradient but in 15 of the 27 with a 20 percent or smaller decrease; the actuarial probability of rebleeding at two years was 0 and 68 percent, respectively (P=0.07).

DISCUSSION

Our results suggest that after an acute episode of variceal bleeding has been controlled, therapy with nadolol plus isosorbide mononitrate has substantial advantages over injection sclerotherapy. The rebleeding rates in our sclerotherapy group were similar to those previously reported at our center^{19,23} and elsewhere.^{3,4}

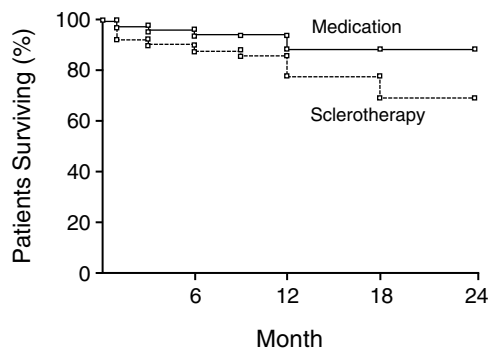


NO. OF PATIENTS AT RISK

Medication group	43	35	28	18	8
Sclerotherapy group	43	23	16	13	6

Figure 1. Actuarial Probability of Remaining Free of Rebleeding in the Medication and Sclerotherapy Groups.

The probability of remaining free of rebleeding was significantly higher among the patients treated with nadolol plus isosorbide mononitrate than among those treated with sclerotherapy (P=0.001). The difference was also significant when the seven patients in the medication group who did not receive nadolol because of contraindications (in three patients) or complications (in four) were not included in the analysis (P=0.003). (Two of these seven patients had rebleeding.)



NO. OF PATIENTS AT RISK

Medication group	43	41	34	23	14
Sclerotherapy group	43	39	29	21	12

Figure 2. Actuarial Probability of Survival in the Medication and Sclerotherapy Groups.

The difference between the groups was not significant ($P = 0.07$).

However, rebleeding was significantly less common with combined-medication therapy, whether all the episodes related to portal hypertension are considered or only those due to esophageal varices. Many factors related to rebleeding were also significantly improved (Table 3). The value of combined therapy with beta-blockers and isosorbide mononitrate was also demonstrated in a trial comparing this treatment with shunt placement for patients in Child-Pugh class A or B and sclerotherapy for those in class C.²⁴ Similar results were obtained with the medical and invasive treatments.²⁴

The benefits of combined-drug therapy in our study were not due to differences between the groups in factors that are important in predicting recurrent variceal hemorrhage, such as the severity of liver disease, the interval from the index bleeding episode to the start of the analysis, the treatment used to stop acute episodes of bleeding, or whether or not the patient has abstained from the use of alcohol.^{1,25,26} Both groups were well matched with respect to these prognostic variables.

The pharmacologic treatment of portal hypertension is based on the assumption that a sustained reduction in portal pressure reduces the incidence of variceal hemorrhage.²⁷ A hepatic venous pressure gradient of 12 mm Hg has been identified as the threshold for the development of variceal hemorrhage.²⁸ Once the gradient has been reduced to a level below 12 mm Hg, patients are protected from a first variceal hemorrhage and have a significant increase in survival.²⁹ However, such a reduction in the hepatic venous pressure gradient is achieved in only a minority of patients.²⁹ After an episode of variceal bleeding, a reduction to a level more than 20 percent below the base-line value, even if the final value is above 12 mm Hg, significantly decreases the risk of rebleeding.³⁰ We found that the proportion of patients with a decrease of more than 20 percent in the base-line hepatic venous pressure gradient and the proportion with values that were reduced to a level below 12 mm Hg were significantly higher in the medication group than in the sclerotherapy group. In the third

month of follow-up, the hepatic venous pressure gradient was an independent predictor of rebleeding. The greater efficacy of medical therapy may be related to the sustained reduction in portal pressure. Our results also indicate that hemodynamic measurements may be useful in identifying patients with a poor response to combined pharmacologic treatment, who may benefit from alternative therapy.

We also found that the incidence of treatment-related complications was significantly lower in the patients treated with nadolol plus isosorbide mononitrate than in those undergoing sclerotherapy. In patients with cirrhosis, nitrates may have deleterious effects on kidney function and on the control of ascites.³¹⁻³³ As in previous studies,^{34,35} however, our results suggest that the combination of a beta-blocker and isosorbide mononitrate does not impair renal function or the control of ascites. It has also been suggested that the prevalence of portal hypertensive gastropathy may be related to sclerotherapy.³⁶ In accordance with this proposed association, we found that the patients treated with sclerotherapy had a significantly higher frequency of portal hypertensive gastropathy than those treated with medications.

In conclusion, we found that therapy with nadolol plus isosorbide mononitrate, as compared with sclerotherapy, significantly decreased the incidence of variceal rebleeding and treatment-related complications. There was also a trend toward improved survival, although the difference between the groups was not significant.

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