

ENDOSCOPIC LIGATION COMPARED WITH COMBINED TREATMENT WITH NADOLOL AND ISOSORBIDE MONONITRATE TO PREVENT RECURRENT VARICEAL BLEEDING

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ABSTRACT

Background After an episode of acute bleeding from esophageal varices, patients are at high risk for recurrent bleeding and death. We compared two treatments to prevent recurrent bleeding — endoscopic ligation and combined medical therapy with nadolol and isosorbide mononitrate.

Methods We randomly assigned 144 patients with cirrhosis who were hospitalized with esophageal variceal bleeding to receive treatment with endoscopic ligation (72 patients) or the combined medical therapy (72 patients). Sessions of ligation were repeated every two to three weeks until the varices were eradicated. The mean (\pm SD) dose of nadolol was 96 ± 56 mg per day, and the mean dose of isosorbide was 66 ± 22 mg per day. The primary end points were recurrent bleeding, complications, and death.

Results The median follow-up period was 21 months. A total of 35 patients in the ligation group and 24 in the medication group had recurrent bleeding. The probability of recurrence was lower in the medication group, both for all episodes related to portal hypertension ($P=0.04$) and for recurrent variceal bleeding ($P=0.04$). There were major complications in nine patients treated with ligation (seven had bleeding esophageal ulcers and two had aspiration pneumonia) and two treated with medication (both had bradycardia and dyspnea) ($P=0.05$). Thirty patients in the ligation group died, as did 23 patients in the medication group ($P=0.52$). The probability of recurrent bleeding was lower for patients with a hemodynamic response to therapy, defined as a decrease in the hepatic venous pressure gradient of more than 20 percent from the base-line value or to less than 12 mm Hg (18 percent, vs. 54 percent in patients with no hemodynamic response at one year; $P<0.001$), and the probability of survival was higher (94 percent vs. 78 percent at one year, $P=0.02$).

Conclusions Combined therapy with nadolol and isosorbide mononitrate is more effective than endoscopic ligation for the prevention of recurrent bleeding and is associated with a lower rate of major complications. (N Engl J Med 2001;345:647-55.)

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AFTER an episode of acute esophageal variceal bleeding, patients are at high risk for recurrent bleeding and death.^{1,2} Thus, therapy to prevent recurrent bleeding is essential.³ Endoscopic sclerotherapy is of proven benefit in such cases.⁴ However, it is associated with a rate of recurrent bleeding of up to 50 percent and with local and systemic complications such as fever, pain, pulmonary infections, and esophageal ulceration, stricture, and perforation. Some of these complications may be fatal.⁵ Endoscopic variceal ligation is a purely mechanical method of obliterating varices that was introduced to preclude the undesirable effects of sclerotherapy.^{6,7} Several studies have shown that, as compared with sclerotherapy, variceal ligation is safer, requires fewer sessions to obliterate varices, significantly reduces the rate of recurrent bleeding, and improves the probability of survival.⁸⁻¹⁰ Accordingly, endoscopic ligation is currently the preferred endoscopic treatment for preventing recurrent variceal bleeding.¹¹

Randomized, controlled trials have shown that sclerotherapy is slightly more effective than nonselective beta-blockers for the prevention of recurrent bleeding, but that in patients treated endoscopically, severe complications are more common. There is no difference in survival.⁵ Hemodynamic studies have demonstrated that the use of nitrates in addition to beta-blockers leads to greater reductions in portal pressure¹² and that such combined therapy is also effective in patients who do not have a response to beta-blockers alone.¹³ Combined treatment with nadolol and isosorbide mononitrate is associated with a significantly lower risk of recurrent bleeding and complications than sclerotherapy.¹⁴ In this study, we compared endoscopic ligation with treatment with nadolol plus isosorbide mononitrate for the prevention of recurrent variceal bleeding.

METHODS

Selection of Patients

Between May 1994 and February 1999, 1318 patients were admitted to our hospital because of gastrointestinal bleeding. Of these, 233 patients with cirrhosis underwent emergency endoscopy within the first 24 hours after admission, and a hemorrhage from esophageal varices was identified. Cirrhosis was diagnosed on the basis

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of a previous liver biopsy or clinical, biochemical, and ultrasonographic findings.

A total of 83 patients were excluded from the trial because of an age of less than 18 years (2 patients), poor hepatic function as indicated by a Child–Pugh score greater than 12 (19 patients), advanced hepatocellular carcinoma (8 patients), associated conditions leading to a life expectancy of six months or less (6 patients), previous endoscopic therapy (16 patients), previous surgery to establish a shunt (2 patients), previous treatment with beta-blockers and isosorbide mononitrate (12 patients), and failure of medical therapy in controlling the index bleeding (18 patients). An additional six patients declined to participate in the study.

Randomization and Treatment

On their fifth day of hospitalization, the remaining 144 patients were randomly assigned to one of two treatment groups with the use of opaque, sealed envelopes that contained a treatment assignment derived from computer-generated random numbers. Randomization was stratified both according to the severity of liver failure (assessed by means of the Child–Pugh classification system [class A or B, indicating moderate failure, vs. class C, indicating severe failure]) and according to whether there was a history of previous 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.

Continuous pharmacologic therapy was started immediately after randomization in the patients assigned to medical treatment. Nadolol was given orally at an initial dose of 80 mg once daily. The dose was subsequently adjusted over a period of five days to reduce the resting heart rate by 25 percent but not below 55 beats per minute. Oral isosorbide mononitrate was started immediately thereafter. Over the course of one week, the dose was progressively increased from 20 mg once a day at bedtime to 40 mg twice a day, unless side effects such as headache or hypotension (systolic blood pressure of less than 85 mm Hg) appeared, in which case we gave the maximal dose tolerated. Adherence to the regimen was assessed at each follow-up visit through careful questioning of the patient and his or her relatives.

Ligation was performed with the use of commercial devices — either a single band with an overtube or a multiband ligating device. Each varix was ligated at least once. Up to eight bands per session were placed within the lower esophagus. Sessions were conducted at the time of randomization, on day 7, and every two to three weeks thereafter until the varices had been eradicated. The varices were considered to have been eradicated when they had either disappeared or could not be grasped and banded by the ligator. Three months after the varices had been eradicated, follow-up endoscopy was performed and additional sessions of ligation were conducted if varices had reappeared; this process was repeated every six months thereafter.

Follow-up and End Points

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

Recurrent bleeding was defined as any episode of hematemesis, melena, or both that occurred during the follow-up period and was evaluated by emergency endoscopy. In both treatment groups, during the index hemorrhage as well as episodes of recurrent bleeding, patients were treated with somatostatin, emergency sclerotherapy, or both. Treatment failure was defined as the occurrence of two or more episodes of recurrent bleeding that required the transfusion of at least 2 units of red cells or a hemorrhage that continued despite medical treatment and required the transfusion of 4 or more units. Patients in whom the protocol treatment failed received an alternative treatment that was determined on a case-by-case basis.

Hemodynamic Studies

Hemodynamic studies were performed before randomization and again one to three months after the start of medical treatment or

once the ligation treatments had been completed. After an overnight fast, a venous-catheter introducer was placed in the right femoral vein by the Seldinger technique and was used to advance, under fluoroscopic guidance, a 7-French balloon catheter into the right main hepatic vein and a Swan–Ganz catheter into the pulmonary artery. Portal pressure was measured as the hepatic venous pressure gradient. A hemodynamic response to therapy was defined as a decrease in the hepatic venous pressure gradient to less than 12 mm Hg or a decrease of more than 20 percent from the base-line value. Cardiopulmonary pressures and cardiac output were also measured. All measurements were performed in triplicate with the use of a previously calibrated strain-gauge transducer.

Statistical Analysis

The sample size was calculated on the assumption that there would be a 26 percent rate of recurrent bleeding in the medication group.¹⁴ In order to detect a difference between groups of at least 21 percent⁷ with use of a two-tailed test, at an alpha level of 0.05 and a beta level of 0.2, we required 70 patients in each treatment group.

All analyses were conducted according to the intention-to-treat principle. Qualitative variables were compared by means of Fisher's exact test. Student's t-test was used to compare continuous variables, and the Wilcoxon rank-sum test was used for skewed or ordinal data.¹⁵ Actuarial probabilities were calculated by the Kaplan–Meier method and compared with use of the log-rank test.¹⁶ Data were censored at the time of death or at the time of the last visit. The Cox proportional-hazards model was used to identify the variables that best explained the variability in the rates of survival and recurrent bleeding.¹⁷ All P values were two-tailed.¹⁵ Calculations were performed with the SPSS statistical software package (SPSS, Chicago).

RESULTS

A total of 72 patients were randomly assigned to each treatment group. Base-line data were similar in the two groups (Tables 1 and 2). The median follow-up period was 21 months (Table 1). Six patients in the medication group had contraindications to nadolol and received only isosorbide mononitrate. There were no patients with contraindications to therapy with isosorbide mononitrate or to ligation. Four patients in the medication group did not adhere to the treatment regimen. Three patients in the ligation group declined further treatment. One stopped treatment after two sessions of ligation, and two stopped after three sessions.

Recurrent Bleeding

The likelihood of recurrent bleeding was significantly lower in the medication group (Fig. 1). The difference was also significant in an analysis that excluded the 12 patients in the medication group who did not receive nadolol because of contraindications (6 patients), complications (2 patients), or nonadherence (4 patients) and the 3 patients in the ligation group who declined to complete the treatment ($P=0.01$); 11 of these 15 patients (8 in the medication group and 3 in the ligation group) had recurrent bleeding episodes.

When the analysis was stratified according to the Child–Pugh class of cirrhosis, the probability of recurrent bleeding at two years was 21 percent in the medication group and 43 percent in the ligation group

among patients in class A ($P=0.05$), 33 percent and 50 percent, respectively, among patients in class B ($P=0.15$), and 53 percent and 63 percent, respectively, among patients in class C ($P=0.64$). The global P value for the analysis of recurrent bleeding according to the base-line Child–Pugh class was 0.04 by the log-rank test. Esophageal varices were the most frequent site of recurrent bleeding (Table 3). The probability of recurrent variceal bleeding was also lower in the medication group (Fig. 1).

In the Cox regression analysis, the treatment-group assignment was an independent predictor of the risk of recurrent bleeding ($P=0.03$), as were the presence or absence of a hemodynamic response ($P<0.001$) and the Child–Pugh score at the third month of follow-up ($P=0.01$).

The likelihood of treatment failure at two years was significantly lower in the medication group: 17 percent, as compared with 36 percent in the ligation group ($P=0.04$). Treatment failed in 12 patients in the medication group; 6 of these patients were then treated with endoscopic ligation, 3 received a transjugular intrahepatic portosystemic shunt, 1 received a portacaval shunt, and the remaining 2 received no further treatment because they had end-stage liver disease. In the ligation group, treatment failed in 23 patients; 8 of these patients were subsequently treated with nadolol and isosorbide mononitrate, 7 received a transjugular intrahepatic portosystemic shunt, 5 received a portacaval shunt, and the remaining 3 received no other treatment.

Survival

The actuarial probability of survival was similar in the two groups. At two years, the probability was 74 percent in the medication group and 65 percent in the ligation group ($P=0.52$). Thirty patients in the ligation group died, as did 23 in the medication group. Of these, 22 patients (12 in the ligation group and 10 in the medication group) died of liver failure. Death was related to recurrent bleeding in 14 patients (10 in the ligation group and 4 in the medication group) and to hepatocellular carcinoma in 13 patients (6 in the ligation group and 7 in the medication group); death was not related to cirrhosis in the remaining 4 patients. In the medication group, one patient died of cancer of the oropharynx and one of hemorrhagic stroke. In the ligation group, one patient died of pancreatic cancer and one of cardiovascular disease. Cox proportional-hazards regression analysis showed that a high Child–Pugh score at the third month of follow-up ($P<0.001$) and treatment failure ($P=0.02$) were independent predictors of death.

Complications and Secondary Outcome Measures

Severe treatment-related complications occurred in nine patients (12 percent) in the ligation group (seven had bleeding esophageal ulcers, and two had aspiration

TABLE 1. CHARACTERISTICS OF PATIENTS TREATED WITH NADOLOL PLUS ISOSORBIDE MONONITRATE OR WITH ENDOSCOPIC LIGATION, AT ADMISSION AND DURING FOLLOW-UP.*

CHARACTERISTIC	LIGATION GROUP (N=72)	MEDICATION GROUP (N=72)
Base line		
Age — yr	58±14	60±12
Sex — no.		
Male	47	43
Female	25	29
Cause of cirrhosis — no. (%)		
Alcoholism	30 (42)	33 (46)
Virus	26 (36)	24 (33)
Alcoholism plus virus	13 (18)	10 (14)
Child–Pugh score	8.4±1.9	7.9±1.9
Child–Pugh class — no.†		
A	11	19
B	43	39
C	18	14
Previous bleeding — no. (%)	7 (10)	10 (14)
Active hemorrhage — no. (%)	26 (36)	28 (39)
Associated diseases — no. (%)	34 (47)	36 (50)
Treatment of index episode — no. (%)		
Somatostatin alone	24 (33)	21 (29)
Sclerotherapy plus somatostatin	43 (60)	44 (61)
Balloon tamponade, sclerotherapy, and somatostatin	5 (7)	7 (10)
Transfusions during index episode (units of packed red cells)		
Mean	2.7±2.4	2.9±2.7
Median	2	2
Range	0–11	0–15
Ascites — no. (%)	50 (69)	47 (65)
Encephalopathy — no. (%)	12 (17)	11 (15)
Variceal grade — no.‡		
1	1	2
2	49	41
3	22	29
Biochemical values§		
Bilirubin — mg/dl	3.2±3.6	2.4±2.1
Albumin — g/liter	30±5	31±5
Prothrombin activity — %	66±16	69±13
Creatinine — mg/dl	0.9±0.2	1.0±0.4
Follow-up		
Abstinence from alcohol — no./total no. with alcoholism	31/43	35/43
Hepatocellular carcinoma — no. (%)	13 (18)	9 (12)
Liver transplantation — no. (%)¶	6 (8)	4 (6)
Duration of follow-up — mo.		
Mean	25±18	23±16
Median	22	20
Range	1–68	1–65
Loss to follow-up — no. (%)**	3 (4)	6 (8)

*Plus-minus values are means ±SD. No differences between 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).

‡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.

¶Ten patients were referred for orthotopic liver transplantation between 7 and 58 months of follow-up.

||The three patients in whom the follow-up period was only one month (two in the ligation group and one in the medication group) died.

**Three patients in the ligation group were lost to follow-up between 8 and 41 months, and six patients in the medication group were lost to follow-up between 6 and 23 months.

TABLE 2. CHANGES IN HEMODYNAMIC VARIABLES, CHILD-PUGH SCORES, AND PLASMA UREA AND CREATININE LEVELS IN THE TWO TREATMENT GROUPS.*

VARIABLE	LIGATION GROUP			MEDICATION GROUP			P VALUE FOR COMPARISONS BETWEEN GROUPS AT 3 MO
	BASE LINE	1-3 MO	P	BASE LINE	1-3 MO	P	
			VALUE FOR CHANGE			VALUE FOR CHANGE	
Hepatic venous pressure (mm Hg)							
Wedge	27.8±3.5	26.3±3.3	0.009	27.8±5.7	23.5±4.7	<0.001	0.01
Free	8.0±2.9	7.1±2.7	0.04	8.1±3.3	7.8±3.2	0.53	0.46
Gradient	19.8±2.9	19.2±3.3	0.21	19.9±3.5	15.9±3.6	<0.001	<0.001
Cardiac output (liters/min)	7.6±2.3	6.5±1.9	<0.001	7.4±2.7	5.1±2.0	<0.001	0.002
Mean arterial pressure (mm Hg)	78.6±7.8	79.2±7.4	0.42	81.8±6.2	79.0±10	0.05	0.92
Heart rate (beats/min)	85±12	75±11	<0.001	85±13	61±10	<0.001	<0.001
Pulmonary wedge pressure (mm Hg)	6.4±2.9	7.8±2.5	<0.001	7.6±3.2	8.1±3.1	0.23	0.73
Right atrial pressure (mm Hg)	3.2±1.9	4.0±2.1	<0.001	3.6±2.4	3.9±2.7	0.35	0.78
Child-Pugh score	8.4±1.9	7.5±2.3	<0.001	7.9±1.9	6.8±2.0	<0.001	0.04
Plasma urea (mg/dl)†	55±30	47±36	0.006	53±30	47±36	0.04	0.93
Plasma creatinine (mg/dl)‡	0.9±0.2	1.1±0.4	0.02	1.0±0.4	1.1±0.5	0.06	0.97

*Plus-minus values are means ±SD.

†To convert the values for urea to millimoles per liter, multiply by 0.166.

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

pneumonia), as compared with two patients (3 percent) in the medication group (both had bradycardia and dyspnea, and nadolol had to be discontinued) ($P=0.05$). In the ligation group, transient dysphagia occurred in five patients, postprocedural pain in six, and fever in two. In the medication group, weakness occurred in seven patients, headache in six, bradycardia in two, and impotence in two. Overall, complications occurred in 22 patients in the ligation group (31 percent) and in 19 in the medication group (26 percent, $P=0.71$). None of the complications were fatal.

At the time of the index endoscopy, six patients in each group had moderate portal hypertensive gastropathy. At the last endoscopy performed during follow-up, 13 patients in the ligation group, as compared with 4 in the medication group, had moderate or severe portal hypertensive gastropathy ($P=0.03$ for the comparison between treatment groups). Kidney function remained within the normal range in both groups, and variations were of similar magnitude (Table 2). During follow-up, ascites developed in 39 patients in the medication group (6 of whom had no history of ascites) and in 47 patients in the ligation group (4 of whom had no history of ascites) ($P=0.23$).

Hemodynamic Measurements

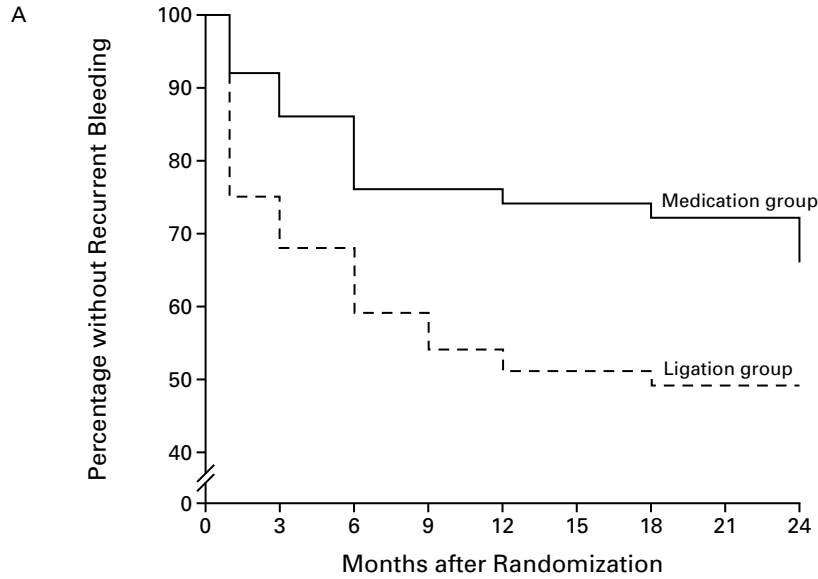
A total of 46 patients in the ligation group and 49 patients in the medication group underwent two he-

modynamic studies each. In the remaining patients, the second study could not be conducted because of previous treatment failure or denial of consent.

Continued medical therapy, but not ligation, significantly reduced the hepatic venous pressure gradient (Table 2). Seven of the 46 patients in the ligation group with two measurements of the hepatic venous pressure gradient (15 percent) had a hemodynamic response, as did 25 of the 49 patients in the medication group with two measurements (51 percent, $P<0.001$). The hepatic venous pressure gradient decreased to less than 12 mm Hg in seven patients in the medication group and one in the ligation group ($P=0.05$).

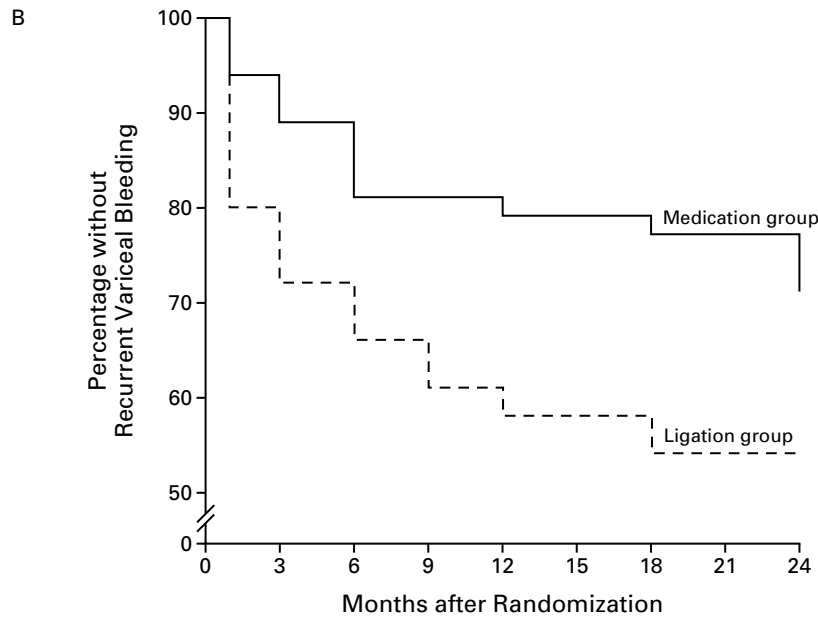
In the medication group, recurrent bleeding occurred in 4 of the 25 patients with a measured hemodynamic response and in 16 of the 24 patients with no response; in the ligation group the comparable figures were 1 of 7 patients and 23 of 39 patients. The likelihood of recurrent bleeding at two years was significantly lower among patients with a hemodynamic response than among those with no response (Fig. 2), both in the medication group (19 percent vs. 62 percent, $P=0.001$) and in the ligation group (15 percent vs. 64 percent, $P=0.05$).

Ascites developed in 6 of the 32 patients with a hemodynamic response, as compared with 42 of the 63 patients with no response ($P<0.001$). Eight of



No. AT RISK

Medication group	72	65	55	43	40	38	33	26	20
Ligation group	72	49	42	34	28	23	20	19	17



No. AT RISK

Medication group	72	65	56	45	42	39	36	26	22
Ligation group	72	53	46	38	32	26	23	22	19

Figure 1. Actuarial Probability of Remaining Free of Any Recurrent Bleeding (Panel A) and Recurrent Variceal Bleeding (Panel B) in the Medication Group and in the Ligation Group.

The probability of remaining free of any recurrent bleeding was significantly higher among the patients treated with nadolol and isosorbide mononitrate than among those treated with ligation ($P=0.04$). The probability of remaining free of recurrent variceal bleeding was also significantly higher among the patients treated with medication than among those treated with ligation ($P=0.04$).

TABLE 3. EPISODES OF RECURRENT BLEEDING IN THE TWO TREATMENT GROUPS.*

VARIABLE	LIGATION GROUP (N=72)	MEDICATION GROUP (N=72)	P VALUE
Patients with recurrent bleeding — no. (%)†	35 (49)	24 (33)	0.04
Total no. of episodes	60	38	
No. of episodes per patient	0.8±1.1	0.5±0.8	0.06‡
Recurrent-bleeding index§	16.6±14.1	18.7±15.2	0.05
Site of recurrent bleeding — no. (%)			
Esophageal varices¶	32 (44)	20 (28)	0.04
Esophageal ulcer	7 (10)	0	0.006
Portal hypertensive gastropathy	1 (1)	1 (1)	0.97
Gastric varices	1 (1)	1 (1)	0.95
Undetermined**	3 (4)	5 (7)	0.62
Other††	2 (3)	2 (3)	0.89
Red cells transfused — units			0.06
Mean	3.1±4.4	1.5±4.0	
Median	0	0	
Range	0–21	0–17	
Treatment failure — no. (%)	23 (32)	12 (17)	0.04
Days of hospitalization	36±26	28±27	0.12‡
No. of hospital admissions not due to bleeding — no. (%)	35 (49)	33 (46)	0.87‡

*Plus-minus values are means ±SD. The mean (±SD) dose of nadolol was 96±56 mg per day, and the mean dose of isosorbide mononitrate was 66±22 mg per day. The mean number of banding sessions was 3.4±1.6 (range, 1 to 9). P values for the comparison between groups were obtained by the log-rank test, except where indicated.

†Three additional patients (two in the medication group and one in the ligation group) had recurrent bleeding from a peptic ulcer. When these patients were included in the analysis, the P value was 0.05.

‡The P value for the comparison between groups was obtained by the Wilcoxon rank-sum test.

§The recurrent-bleeding index was calculated for each patient by dividing the months of follow-up by the number of episodes of recurrent bleeding plus 1. This index reflects the time during which each patient was free of recurrent bleeding during the follow-up period.

¶In the medication group, 20 patients had a total of 29 episodes of recurrent bleeding from esophageal varices. In the ligation group, 32 patients had a total of 45 episodes of recurrent bleeding from esophageal varices.

||In the ligation group, seven patients had eight episodes of recurrent bleeding from esophageal ulcers.

**In three patients (two in the medication group and one in the ligation group), more than one potential site of bleeding was apparent on endoscopy, and five patients (three in the medication group and two in the ligation group) did not undergo endoscopy.

††Two patients (one in each group) had reflux esophagitis, one patient in the medication group had duodenal varices, and one patient in the ligation group had Mallory-Weiss tears.

the 32 patients with a response had to be admitted to the hospital for reasons other than hemorrhage, as compared with 30 of the 63 patients with no response (P=0.04). At the third month of follow-up, the Child-Pugh score was lower among the patients with a hemodynamic response (6.1±1.8 vs. 7.1±2.0, P=0.01). The actuarial probability of survival was significantly higher among the patients with a hemodynamic response than among those with no response (P=0.02) (Fig. 2). A total of 24 of the 63 patients

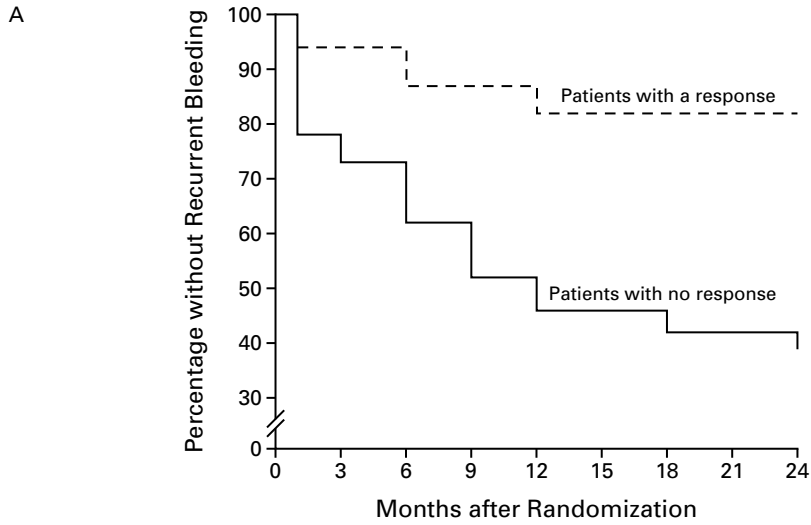
with no hemodynamic response (38 percent) and 3 of the 32 patients with a response (9 percent) died. Stepwise logistic-regression analysis showed that the treatment-group assignment (P=0.01) and the Child-Pugh score at the third month of follow-up (P=0.05) were independent predictors of the likelihood of a hemodynamic response.

DISCUSSION

The efficacy of variceal ligation, as found in our study, is consistent with the higher ranges previously reported in randomized trials of this treatment.¹⁸⁻²⁰ A relatively wide variation in rates of recurrent bleeding has been observed with ligation.^{8-10,18-20} This variation may be due, at least in part, to technical differences among studies, such as variations in the interval between sessions or in the number of bands placed during each session.¹¹ Whether these or other technical differences can affect the outcome has not been adequately investigated. Other possible confounding factors — such as the time since the initial bleeding episode, alcohol use or nonuse, and the treatment used to stop the bleeding — may also affect the results of treatment.^{2,3,21} Among different trials, there may be differences in the randomization process or in the characteristics of the population treated, such as the cause or the severity of cirrhosis,² or in the definition of end points such as recurrent bleeding.^{3,22}

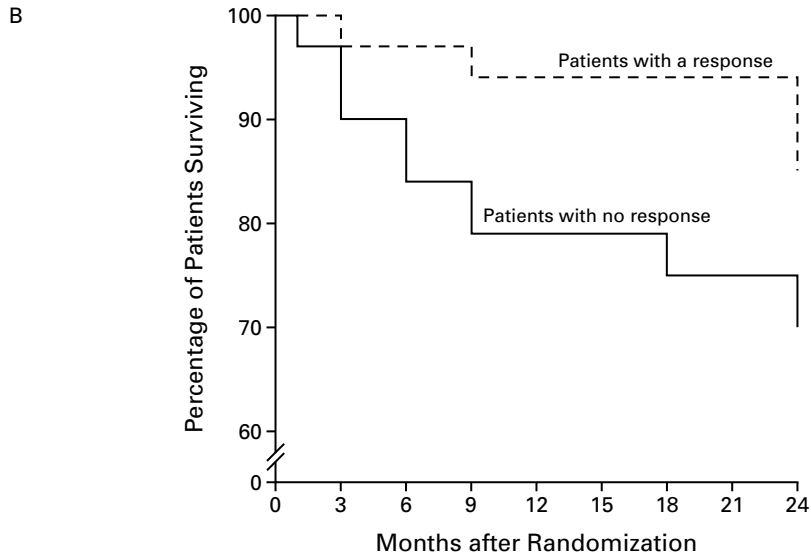
Our study had few exclusion criteria; a high proportion of the patients had advanced liver disease; and randomization was performed soon after the initial episode of acute bleeding had been controlled. All the episodes of recurrent bleeding were evaluated, regardless of the severity or the source (even those of unknown origin were taken into account), and the treatment of both the index episode of bleeding and recurrent hemorrhages included emergency sclerotherapy instead of ligation. These factors may account for the relatively high rate of recurrent bleeding in the ligation group. Although this rate of recurrent bleeding may seem similar to our previous findings with sclerotherapy in a study with a similar design,¹⁴ the studies are not comparable. The current study had a longer follow-up period, and the patients were sicker, as indicated by factors such as higher portal pressure and higher Child-Pugh score at follow-up.

The efficacy of the combination of a beta-blocker and isosorbide mononitrate was similar to that previously reported.²³ Our results suggest that once acute esophageal variceal bleeding has been controlled, this combined medical therapy has significant advantages over endoscopic ligation. Recurrent bleeding was significantly less common with the medical therapy — whether we considered all the episodes related to portal hypertension or only those caused by esophageal varices. The difference was more pronounced among patients whose liver function was well preserved. Furthermore, although the incidence of side effects was



NO. AT RISK

Patients with a response	32	29	27	23	22	20	15	13	10
Patients with no response	63	46	38	29	25	21	19	17	15



NO. AT RISK

Patients with a response	32	31	30	25	24	20	17	15	11
Patients with no response	63	60	55	50	45	42	39	35	32

Figure 2. Actuarial Probability of Remaining Free of Recurrent Bleeding (Panel A) and of Survival (Panel B), According to the Presence or Absence of a Hemodynamic Response.

Among the 95 patients in whom two hemodynamic studies were conducted (49 patients in the medication group and 46 in the ligation group), 32 patients had a reduction in the hepatic venous pressure gradient to less than 12 mm Hg or a reduction of more than 20 percent from the base-line value and were therefore considered to have had a hemodynamic response to therapy; the remaining 63 patients were considered to have had no response. The probability of recurrent bleeding was significantly lower among those who had a response than among those who did not ($P < 0.001$). The probability of survival was significantly higher among those who had a response than among those who did not ($P = 0.02$). During the follow-up period, 24 of the 63 patients who did not have a hemodynamic response died (38 percent), as did 3 of 32 patients who had a response (9 percent).

similar in the two treatment groups, the rate of major complications was significantly lower among patients who received medical therapy than among those treated with endoscopic ligation. With both treatments, the incidence and types of complications were similar to those reported in previous trials.^{11,23} As in previous studies,^{24,25} our results show that the combination of a beta-blocker and isosorbide mononitrate does not impair renal function or increase the risk of ascites. It has also been suggested that, as with sclerotherapy,⁵ variceal ligation may worsen the severity of portal hypertensive gastropathy.²⁶ We found that this condition developed in patients treated with ligation significantly more often than in those treated with medications.

Combined therapy with beta-blockers plus isosorbide mononitrate was compared with endoscopic variceal ligation for the prevention of recurrent variceal bleeding in another study; its preliminary results are similar to ours.²⁷ A recent randomized trial also suggests that the addition of isosorbide mononitrate to beta-blockers improves the efficacy of the beta-blockers in the prevention of recurrent variceal bleeding in patients with cirrhosis.²⁸ Furthermore, no clear advantages have been noted in trials in which the use of a transjugular intrahepatic portosystemic shunt²⁹ or invasive therapy (consisting of surgery to establish a shunt for patients in Child–Pugh class A or B, and sclerotherapy for patients with class C disease)³⁰ has been compared with this combined medical therapy.

The higher efficacy we observed with medical therapy may be related to hemodynamic changes.³¹ Pharmacologic therapy aims to produce a sustained reduction in portal pressure.³² The response of portal pressure to treatment can be considered appropriate when the hepatic venous pressure gradient is reduced to less than 12 mm Hg or by more than 20 percent from the base-line value.^{31,33,34} The risk of variceal bleeding is extremely low when these targets are achieved.^{33,34} In our trial, the proportion of patients who had a hemodynamic response was significantly higher with medical therapy than with ligation. In both treatment groups, the probability of recurrent bleeding was significantly lower among patients who had a hemodynamic response than among those who did not. The probability of survival was also significantly higher among the patients with a hemodynamic response than among those with no response. A hemodynamic response was an independent predictor of the risk of recurrent bleeding, and treatment failure was an independent predictor of death.

In conclusion, in comparison with endoscopic ligation, we found that combined therapy with nadolol and isosorbide mononitrate significantly decreases the incidence of recurrent bleeding and of the major treatment-related complications of variceal hemorrhage. Our data suggest that monitoring of the hepatic venous pressure gradient identifies patients with a poor

response, in whom more aggressive alternative therapies may be warranted.

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REFERENCES

- Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981;80:800-9.
- Burroughs AK, McCormick PA. Natural history and prognosis of variceal bleeding. *Baillieres Clin Gastroenterol* 1992;6:437-50.
- Grace ND, Groszmann RJ, Garcia-Tsao G, et al. Portal hypertension and variceal bleeding: an AASLD single topic symposium. *Hepatology* 1998;28:868-80.
- Balanzó J, Such J, Sáinz S, et al. Long term survival and severe rebleeding after variceal sclerotherapy. *Surg Gynecol Obstet* 1990;171:489-92.
- D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995;22:332-54.
- Van Stiegmann G, Cambre T, Sun JH. A new endoscopic elastic band ligating device. *Gastrointest Endosc* 1986;32:230-3.
- Van Stiegmann G, Goff JS, Sun JH, Hruza D, Reveille RM. Endoscopic ligation of esophageal varices. *Am J Surg* 1990;159:21-6.
- Stiegmann GV, Goff JS, Michaletz-Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med* 1992;326:1527-32.
- Gimson AES, Ramage JK, Panos MZ, et al. Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices. *Lancet* 1993;342:391-4.
- Laine L, el-Newihi HM, Migikovsky B, Sloane R, Garcia F. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. *Ann Intern Med* 1993;119:1-7.
- Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: a meta-analysis. *Ann Intern Med* 1995;123:280-7.
- García-Pagán JC, Feu F, Bosch J, Rodés J. Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis: a randomized controlled study. *Ann Intern Med* 1991;114:869-73.
- Merkel C, Sacerdoti D, Bolognesi M, et al. Hemodynamic evaluation of the addition of isosorbide-5-mononitrate to nadolol in cirrhotic patients with insufficient response to the β -blocker alone. *Hepatology* 1997;26:34-9.
- Villanueva C, Balanzó J, Novella MT, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996;334:1624-9.
- Armitage P, Berry G. *Statistical methods in medical research*. 3rd ed. Oxford, England: Blackwell Scientific, 1994.
- Altman DG. *Practical statistics for medical research*. London: Chapman & Hall, 1991.
- Christensen E. Multivariate survival analysis using Cox's regression model. *Hepatology* 1987;7:1346-58.
- Jalan R, Forrest EH, Stanley AJ, et al. A randomized trial comparing transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from esophageal varices. *Hepatology* 1997;26:1115-22.
- Gralnek IM, Jensen DM, Kovacs TOG, et al. The economic impact of esophageal variceal hemorrhage: cost-effectiveness implications of endoscopic therapy. *Hepatology* 1999;29:44-50.
- Lo GH, Lai KH, Cheng JS, et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. *Hepatology* 2000;32:461-5.
- Burroughs AK, Mezzanotte G, Phillips A, McCormick PA, McIntyre N. Cirrhotics with variceal hemorrhage: the importance of the time interval between admission and the start of analysis for survival and rebleeding rates. *Hepatology* 1989;9:801-7.
- de Franchis R, Pascal JP, Ancona E, et al. Definitions, methodology and therapeutic strategies in portal hypertension: a consensus development workshop, Baveno, Lake Maggiore, Italy, April 5 and 6, 1990. *J Hepatol* 1992;15:256-61.
- D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999;19:475-505.
- Morillas RM, Planas R, Cabré E, et al. Propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis: long-term hemodynamic and renal effects. *Hepatology* 1994;20:1502-8.
- Merkel C, Gatta A, Donada C, et al. Long-term effects of nadolol or nadolol plus isosorbide-5-mononitrate on renal function and ascites formation in patients with cirrhosis. *Hepatology* 1995;22:808-13.

26. de la Peña J, Rivero M, Sanchez E, Fábrega E, Crespo J, Pons-Romero E. Variceal ligation compared with endoscopic sclerotherapy for variceal hemorrhage: prospective randomized trial. *Gastrointest Endosc* 1999;49:417-23.
27. Patch D, Goulis J, Gerunda G, Merkel C, Greenslade L, Burroughs AK. A randomised controlled trial comparing wedge pressure guided medical therapy (MT) against variceal banding (VB) in the secondary prevention of variceal haemorrhage. *J Hepatol* 2000;32:Suppl 2:35. abstract.
28. Gournay J, Masliah C, Martin T, Perrin D, Galmiche JP. Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Hepatology* 2000;31:1239-45.
29. Escorsell A, Bañares R, Gilibert R, et al. Transjugular intrahepatic portosystemic shunt (TIPS) vs propranolol + isosorbide-mononitrate (P+I) for the prevention of variceal rebleeding in patients with cirrhosis: results of a randomized controlled trial. *Hepatology* 1998;28:Suppl:770A. abstract.
30. McCormick PA, Feu F, Sabrin C, Planas R. Propranolol and isosorbide mononitrate versus sclerotherapy or shunt surgery for the prevention of variceal rebleeding: a randomized trial. *Hepatology* 1994;20:Suppl:106A. abstract.
31. Bosch J, García-Pagán JC. Complications of cirrhosis. I. Portal hypertension. *J Hepatol* 2000;32:Suppl 1:141-56.
32. 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.
33. Groszmann RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990;99:1401-7.
34. Feu F, García-Pagán JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* 1995;346:1056-9.

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