

## COMPARISON OF ENDOSCOPIC LIGATION AND PROPRANOLOL FOR THE PRIMARY PREVENTION OF VARICEAL BLEEDING

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### ABSTRACT

**Background and Methods** We compared propranolol therapy and endoscopic ligation for the primary prevention of bleeding from esophageal varices. This prospective, controlled trial included consecutive eligible patients who had large varices (>5 mm in diameter) that were at high risk for bleeding. The patients were assigned to either propranolol therapy, at a dose sufficient to decrease the base-line heart rate by 25 percent, or variceal ligation, to be performed weekly until the varices were obliterated or so reduced in size that it was not possible to continue treatment.

**Results** Of the 89 patients, 82 of whom had cirrhosis of the liver, 44 received propranolol and 45 underwent variceal ligation. The mean ( $\pm$ SD) duration of follow-up in each group was  $14\pm 9$  and  $13\pm 10$  months, respectively. The mean time required to achieve an adequate reduction in the heart rate was  $2.5\pm 1.7$  days; the mean number of sessions needed to complete variceal ligation was  $3.2\pm 1.1$ . After 18 months, the actuarial probability of bleeding was 43 percent in the propranolol group and 15 percent in the ligation group ( $P=0.04$ ). Twelve patients in the propranolol group and four in the ligation group had bleeding. Three of the four in the ligation group had bleeding before their varices had been obliterated. Nine patients in the ligation group had recurrent varices, a mean of 3.7 months after the initial treatment. Five patients in each group died; bleeding from the varices was the cause of death of four patients in the propranolol group and of three in the ligation group. There were no serious complications of variceal ligation; in the propranolol group, treatment was stopped in two patients because of side effects.

**Conclusions** In patients with high-risk esophageal varices, endoscopic ligation of the varices is safe and more effective than propranolol for the primary prevention of variceal bleeding. (N Engl J Med 1999;340:988-93.)

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**B**LEEDING from esophageal varices is associated with mortality rates ranging from 30 to 70 percent.<sup>1,2</sup> Many therapies have been evaluated for primary prophylaxis against bleeding in people with cirrhosis and large varices.<sup>3-5</sup> The most effective therapy is the use of nonselective beta-blockers, which reduce the incidence of a first bleeding episode and, to some extent, reduce bleeding-related mortality.<sup>5,6</sup> However, beta-blockers have unpredictable effects on the hepatic venous pressure gradient, which is used to assess their efficacy.<sup>7,8</sup> Measurement of this gradient requires an invasive technique in which a catheter is passed through the fem-

oral or jugular vein and wedged into a hepatic vein; the difference between the wedged and free hepatic venous pressures is recorded as the wedged hepatic venous pressure gradient. In one recent study,<sup>9</sup> the requisite reduction of more than 20 percent in the gradient was achieved in only 14 percent of patients who received propranolol. In another study, because of frequent side effects and contraindications, propranolol therapy was found suitable for only 23 percent of patients with cirrhosis.<sup>10</sup> Other issues of concern with respect to the use of beta-blockers are the lack of patient compliance, the prolonged (in some cases lifelong) need for therapy,<sup>11</sup> and the risk of rebleeding after the cessation of therapy.<sup>12</sup> The combination of a beta-blocker and a nitrate has been found superior to monotherapy with propranolol<sup>13</sup> or nadolol.<sup>14</sup> However, prolonged use of nitrates may increase the already advanced vasodilatory state of such patients<sup>15</sup> and increase mortality in patients with cirrhosis who are more than 50 years old.<sup>16</sup>

Endoscopic sclerotherapy is currently not recommended as prophylactic therapy for esophageal varices because of conflicting results in earlier studies.<sup>17-19</sup> Endoscopic variceal ligation is more effective and safer than sclerotherapy<sup>20-22</sup> and decreases the risk of initial bleeding<sup>23</sup> and the risk of death<sup>24</sup> due to varices as compared with no treatment. On the basis of these results, we conducted a prospective, randomized, controlled trial to compare the efficacy and safety of variceal ligation with those of propranolol for the primary prevention of variceal bleeding in patients with esophageal varices that were at high risk for bleeding.

### METHODS

From September 1994 to July 1997, we screened 322 consecutive patients with portal hypertension who had never had bleeding from varices. Eligible patients included those with large, grade 3 or 4 varices as independently evaluated by two endoscopists and no history of hematemesis or melena.<sup>23</sup> The size of the varices was graded according to criteria published by Conn,<sup>25</sup> as follows: 1, small varices detectable only on performance of the Valsalva maneuver; 2, small varices (diameter, approximately 1 to 3 mm) visible during both phases of respiration; 3, varices of 3 to 6 mm; and 4, varices of >6 mm. The size of each varix was assessed by opening biopsy forceps in the lumen of the lower 2 to 3 cm of the esophagus. The risk of bleeding in large varices (>5 mm) was

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assessed by looking for the presence of at least one "red sign," such as a cherry-red spot, a red wale, or a hematocystic spot. The rate of agreement between the two observers with regard to red signs on endoscopy was 94 percent. For the same observer, the rate of agreement between two readings was 95 percent.

Cirrhosis was diagnosed on the basis of clinical, biochemical, histologic, or ultrasonographic evidence. Noncirrhotic portal fibrosis was diagnosed when varices were present and there was no evidence of thrombosis in the splenoportal axis on ultrasonography and no evidence of cirrhosis on liver biopsy.<sup>26</sup> Extrahepatic obstruction of the portal vein was diagnosed when a portal cavernoma was detected by ultrasonography and there were no signs of cirrhosis.<sup>26,27</sup> For all the patients, information on alcohol abuse was obtained, and tests for hepatitis B and C viruses and autoimmune markers in the serum were performed. The severity of liver disease was classified according to Child's criteria. Patients were excluded if they were receiving antiviral therapy or if they had concomitant hepatoma or another tumor, severe cardiopulmonary or renal disease, bradycardia (basal heart rate, <55 beats per minute), bronchial asthma, diabetes mellitus, heart failure, peripheral vascular disease, a psychiatric disorder, glaucoma, or prostatic hypertrophy. Written informed consent was obtained from the patients according to the guidelines of the 1975 Declaration of Helsinki.

Of the 105 patients with varices at high risk for bleeding who were recruited after screening, 90 were eligible for the study. Reasons for ineligibility were contraindications to the use of beta-blockers (eight patients), coexistent hepatoma (five), an inability on the part of the patient to attend follow-up (one), and refusal to follow the treatment protocol (one). Patients were randomly assigned at the time of the first endoscopic examination to undergo ligation or to receive propranolol, according to a table of random numbers.

### Endoscopic Ligation

Patients assigned to the ligation group underwent ligation at the first endoscopy session or within the next 24 hours. After local application of lidocaine, an endoscope (model GIF X-Q 20 or CV-1, Olympus Optical, Tokyo) was introduced, and the ligation was carried out by placing a single rubber band (Bard Interventional Products, Tewksbury, Mass.) over a varix each time the endoscope was inserted. As many bands as possible (average, three to nine bands, with fewer in later sessions) were placed in the lower 5 to 7 cm of all variceal columns (vertical veins). Each residual varix was ligated distally and proximally to accelerate obliteration. A 25-cm-long sheath, supplied with the band-ligation set, was occasionally used as a sleeve over the endoscope to facilitate insertion and removal after the intravenous administration of 2.5 to 5.0 mg of diazepam.

### Propranolol Therapy

Patients assigned to receive propranolol underwent base-line electrocardiography and cardiac evaluation after 15 minutes of rest. Treatment then began with the oral administration of 40 mg of propranolol. The heart rate and blood pressure were checked after 12 and 24 hours. Instead of adjusting the dose by monitoring the hepatic venous pressure gradient, we increased the dose in increments of 20 to 40 mg per day until a 25 percent decrease in the base-line heart rate was achieved. Treatment was stopped if any of the following occurred: systolic blood pressure less than 80 mm Hg, heart rate less than 55 beats per minute, or other serious side effects.

### Follow-up

Patients were followed through July 1997. Endoscopic ligation was performed every week until the varices were obliterated or were reduced to a size of grade 1. In the latter instance, it was not possible to apply any more bands because of the small size of the varices. Patients were asked to record all symptoms, such as chest pain, fever, and dysphagia. The presence of ulcers or strictures was noted on endoscopy. After the varices had been obliterated or reduced in size to grade 1, patients underwent endoscopy monthly for the first three months and then once every three months until

the end of follow-up. If varices recurred and became grade 2 in size or larger, ligation was repeated to obliterate them.

Patients receiving propranolol were monitored daily until beta-blockade was adequate, then monthly for the first three months, and subsequently every three months. Drug compliance was ascertained by interviewing the patient and by measuring the heart rate. Patients were advised to refrain from consuming alcohol and from taking nonsteroidal antiinflammatory drugs, histamine H<sub>2</sub> blockers, or proton-pump inhibitors.

### End Points

The principal end point was bleeding from the varices. Additional end points included death due to variceal bleeding, causes related to the underlying liver disease, or unrelated causes; upper gastrointestinal tract bleeding from causes not related to the varices; or the development of serious side effects that required the discontinuation of therapy.

### Bleeding

Any patient who had overt upper gastrointestinal bleeding during the study was admitted to the hospital and underwent endoscopy of the upper gastrointestinal tract within 24 hours to determine the source of bleeding. Bleeding from esophageal varices was diagnosed if active bleeding or a clot was seen on endoscopy or if there was evidence of recent bleeding in a patient with an esophageal varix and no other visible mucosal lesion. Bleeding was considered to have arisen from gastric varices if active bleeding or a clot was seen on endoscopy or if there was evidence of recent bleeding in a patient with a gastric varix and the bleeding had no other possible cause.<sup>28</sup> Bleeding was considered to be caused by portal hypertensive gastropathy if distinct lesions of the gastric mucosa were present and there was no evidence of bleeding from esophageal, gastric, or ectopic varices.<sup>29</sup> Bleeding was considered to be caused by esophageal ulcers as a result of band ligation if there was active bleeding or if there was an adherent clot on the esophageal ulcer. Bleeding from any source was considered to be serious if the estimated total blood loss was greater than 1500 ml, the heart rate was greater than 100 beats per minute, the systolic blood pressure was less than 100 mm Hg, and the patient required transfusion of more than 4 units of blood in six hours.

### Management of Upper Gastrointestinal Tract Bleeding

All episodes of upper gastrointestinal tract bleeding were managed with supportive therapy, including transfusions of blood and plasma, balloon tamponade, infusion of somatostatin, or emergency ligation. Other complications of liver disease, such as hepatic encephalopathy and spontaneous bacterial peritonitis, were managed according to standard protocols.

### Statistical Analysis

Data were analyzed according to an intention-to-treat strategy. Quantitative data were expressed as means ( $\pm$ SD) or as medians. Student's two-tailed t-test or an appropriate nonparametric test was used to compare values in the two groups. Qualitative data were analyzed by the chi-square test or Fisher's exact test.<sup>30</sup> Agreement between observers with regard to the red signs on endoscopy was measured by the kappa statistic.<sup>31</sup> The actuarial probabilities of bleeding from varices and of death from bleeding or any cause related to liver disease were calculated for all the patients by the Kaplan-Meier method, and comparisons were made with use of the log-rank test.<sup>31</sup> Subgroups were also analyzed, after patients without cirrhosis were excluded. Cox proportional-hazards regression analysis was carried out to assess the effect of confounding variables.<sup>32</sup>

## RESULTS

The 90 eligible patients were randomly assigned to undergo ligation (46 patients) or to receive pro-

pranolol therapy (44 patients). One patient assigned to the ligation group failed to appear the next day and hence was excluded, leaving 45 patients in that group. The patients' characteristics are shown in Table 1. The mean dose of propranolol was  $70 \pm 35$  mg per day, and the time required to achieve an adequate reduction in the heart rate was  $2.5 \pm 1.7$  days. In the ligation group, obliteration of the varices was achieved in all the surviving patients with  $3.2 \pm 1.1$  endoscopy sessions over a period of  $4.1 \pm 2.0$  weeks. The endoscopy session was postponed by one week in the case of four patients because of diffuse ulcerations on the varices. On nine occasions, patients missed an endoscopy appointment. During the study period, bleeding occurred in 12 patients in the propranolol group and 4 in the ligation group (27 per-

cent and 9 percent, respectively). The cumulative probability of variceal bleeding during different follow-up periods is shown in Figure 1. It was 43 percent in the propranolol group and 15 percent in the ligation group after 18 months of follow-up ( $P=0.04$  by the log-rank test). No further events occurred after 18 months of follow-up, although only a few patients were followed for 32 months. The hazard ratio for variceal bleeding in the propranolol group, as compared with the ligation group, was 3.0 (95 percent confidence interval, 1.3 to 9.3). After adjustment for age, the ratio was 2.6 (95 percent confidence interval, 1.0 to 8.2).

In three of the four patients in the ligation group who had bleeding, the bleeding occurred within the first six weeks, before the varices could be eradicated. The bleeding originated from post-ligation ulcers in two patients and from a recurrence of esophageal varices in one patient. In the patients in the propranolol group, bleeding from esophageal varices occurred throughout the treatment period. The severity of bleeding was similar in the two groups. The response to either therapy did not change if gastric varices were present; none of the patients had bleeding from gastric varices.

The 4 patients in the ligation group and 10 of the 12 patients in the propranolol group who had bleeding had advanced liver disease (Child's class B or C). None of the patients with noncirrhotic portal hypertension had bleeding. A subgroup analysis after data on patients without cirrhosis were excluded (leaving 41 patients in each group) showed actuarial probabilities of bleeding of 17 percent in the group undergoing ligation and 43 percent in the group receiving propranolol ( $P=0.08$ ).

Ten patients (five in each group) died, all from disorders involving the liver (Table 2). The number of deaths related to bleeding was similar in the two groups: three patients in the ligation group and four in the propranolol group died from bleeding. The actuarial probability of survival in the ligation and propranolol groups was 88 percent and 82 percent, respectively ( $P=0.98$ ). There was a trend toward fewer hospitalizations in the ligation group, and fewer patients in the ligation group required blood transfusions.

At the end of the follow-up period, 9 of 40 (22 percent) surviving patients in the ligation group had recurrent varices. Varices recurred a mean of  $3.7 \pm 2.1$  months (range, 2 to 13) after the initial obliteration and could be obliterated again in  $1.4 \pm 0.5$  sessions by repeated ligation. Second recurrences were rare during follow-up. In one patient, whose follow-up was irregular, bleeding occurred from large varices after 13 months; this patient subsequently died.

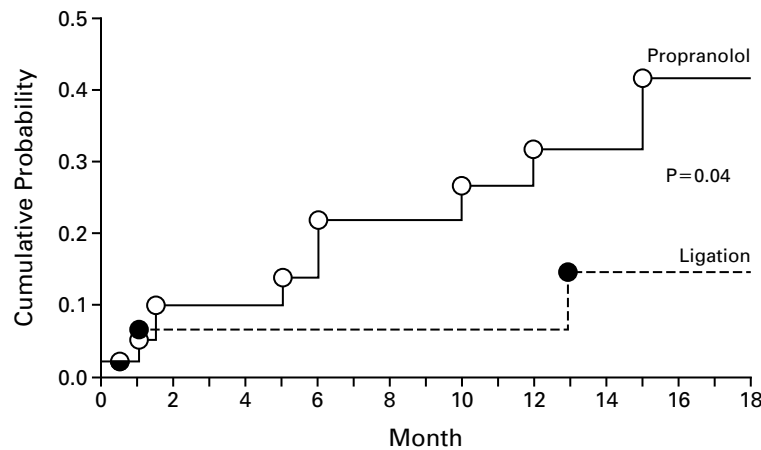
No serious complications resulted from variceal ligation. Transient retrosternal pain, fever, and dysphagia developed in 18 percent, 7 percent, and 4 percent

**TABLE 1.** CHARACTERISTICS OF THE 89 PATIENTS ACCORDING TO STUDY GROUP.\*

CHARACTERISTIC	ENDOSCOPIC LIGATION (N=45)	PROPRANOLOL (N=44)
Age — yr	44±12	39±17
Sex — no. (%)		
Male	33 (73)	32 (73)
Female	12 (27)	12 (27)
Cause of varices — no. (%)		
Cirrhosis	41 (91)	41 (93)
Alcoholic	11	9
Hepatitis B	16	15
Hepatitis C	5	2
Hepatitis B and C	0	1
Autoimmune	2	2
Cryptogenic	7	12
Extrahepatic portal-vein obstruction	3 (7)	3 (7)
Noncirrhotic portal fibrosis	1 (2)	0
Observations on endoscopy — no. of patients (%)		
Grade of varices		
III	32 (71)	34 (77)
IV	13 (29)	10 (23)
Gastric varices		
Before therapy	8 (18)	9 (20)
After therapy	9 (20)	9 (20)
Portal gastropathy		
Before therapy	9 (20)	10 (23)
After therapy	11 (24)	10 (23)
Gastric antral vascular ectasia		
Before therapy	0	2 (5)
After therapy	0	2 (5)
Child's classification — no. (%)		
A	7 (16)	9 (20)
B	23 (51)	22 (50)
C	15 (33)	13 (30)
Ascites — no. (%)	31 (69)	27 (61)
Encephalopathy — no. (%)	7 (16)	6 (14)
Abnormal prothrombin time — no. (%)†	33 (73)	29 (66)
Follow-up — mo	13±10	14±9

\*Plus-minus values are means ±SD.

†The prothrombin time was considered abnormal if it was more than three seconds longer than the control value.



NO. OF PATIENTS AT RISK							
Ligation	45	40	27	16	12	8	7
Propranolol	44	35	28	16	13	7	5
NO. OF PATIENTS WITH FAILURE OF THERAPY							
Ligation	—	3	3	3	3	4	4
Propranolol	—	5	9	9	11	12	12

Figure 1. Cumulative Probability of Variceal Bleeding in the Two Groups of Patients.

of the patients, respectively. Post-ligation variceal ulcers, generally superficial, developed in 36 patients (80 percent) one week after the first session of ligation. Sixteen patients in the propranolol group (36 percent) had one or more side effects possibly related to the drug. These included lethargy in 12 patients, psychiatric disturbances in 4, hypotension in 2, impotence in 2, and bronchospasm in 1. However, in only two of these patients was the therapy stopped, in one because of persistent hypotension, weakness, and lethargy and in the other because of altered sensorium possibly associated with propranolol therapy.

DISCUSSION

Treatment with beta-blockers<sup>5,6</sup> and endoscopic variceal ligation<sup>23</sup> have independently been shown to decrease the risk of a first episode of variceal bleeding. Our study confirmed these observations when the risk of bleeding in patients given either therapy was compared with that in untreated patients described in earlier studies. In one earlier study,<sup>23</sup> we found that the incidence of variceal bleeding in patients with untreated varices at high risk for bleeding was about 39 percent during a mean follow-up period of 14 months. Lay et al. observed incidence rates of variceal bleeding of 40 percent and 60 percent at 12 and 24 months of follow-up, respectively, in patients with untreated cirrhosis who had high-risk varices.<sup>24</sup> With the use of beta-blockers, this risk was decreased to 18 to 25 percent,<sup>33,34</sup> and with the addition of nitrates, to about 8 percent.<sup>16</sup>

We found that the risk of bleeding with ligation was significantly lower than that with propranolol

therapy. The actuarial risk of bleeding at the end of 18 months in the ligation group was 15 percent, a risk similar to that reported previously with drug therapy.<sup>16,33,34</sup> The four patients in the ligation group who had bleeding had advanced liver disease. Severe early rebleeding from esophageal varices after ligation has been reported by Sakai et al.<sup>35</sup> and by Lay et al.<sup>24</sup> in patients with advanced liver disease. Two patients had bleeding from post-ligation ulcers and one from esophageal varices before the varices were obliterated.

TABLE 2. OUTCOMES OF TREATMENT ACCORDING TO STUDY GROUP.

CHARACTERISTIC	ENDOSCOPIC LIGATION (N=45)	PROPRANOLOL (N=44)	P VALUE
Patients hospitalized — no. (%)	5 (11)	12 (27)	0.09
No. of patients needing blood transfusion	1	7	0.03
Mean no. of transfusions per patient	0.1	0.4	0.03
Actuarial probability of survival at 18 mo — %	88	82	0.98
Deaths — no. (%)	5 (11)	5 (11)	0.77
Cause of death — no.			
Bleeding*	3	4	
Spontaneous bacterial peritonitis	1	0	
Hepatic encephalopathy	1	1	
Child's class at time of death — no.			
A	0	0	
B	1	3	
C	4	2	

\*Death was due to massive bleeding or was related to a bleeding event.

ed. Had we treated our patients with sucralfate<sup>36</sup> or omeprazole,<sup>37</sup> the two ulcer-related bleeding episodes might have been prevented. The only patient who had bleeding after variceal obliteration had irregular follow-up and missed a few endoscopy sessions scheduled for surveillance. In this patient, grade 3 varices developed, from which she had fatal bleeding. Varices recurred during follow-up in the ligation group a mean of  $3.7 \pm 2.1$  months (range, 2 to 13) after the initial obliteration. However, after repeated ligation, a second recurrence was rare. We therefore recommend that surveillance endoscopy should first be performed within three months after the obliteration of varices. Subsequently, endoscopy should be performed at six-to-nine-month intervals.

Beta-blocker therapy needs to be given for a prolonged period, possibly for life, and noncompliance raises the risk of bleeding to pretreatment levels.<sup>11,12</sup> In contrast, with ligation, varices can be obliterated within about a month, or possibly earlier, and therefore ligation offers a distinct advantage over lifelong propranolol therapy. Furthermore, no patient in our ligation group had to be excluded, whereas in the propranolol group eight patients had to be initially excluded because of contraindications to the drug and two subsequently withdrawn from therapy because of side effects. Others have also reported a high frequency of side effects, often requiring discontinuation of beta-blockers.<sup>9-14</sup>

The overall mortality in the two groups was similar (11 percent), although fewer patients in the ligation group required blood transfusions and there was a trend in that group toward fewer hospitalizations. Ligation should have a role particularly in the treatment of patients with high-risk varices in whom beta-blockers are contraindicated or must be discontinued because of side effects.<sup>38</sup> Our findings also suggest that the combination of both therapies should be evaluated to determine whether even better results can be achieved.

Part of this work has appeared in abstract form (*Hepatology* 1997;26:360A).

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