Digestive Diseases and Sciences, Vol. 50, No. 8 (August 2005), pp. 1538–1547 (© 2005)
DOI: 10.1007/s10620-005-2877-1

Evaluation of Endoscopic Variceal Ligation (EVL) Versus Propanolol Plus Isosorbide Mononitrate/Nadolol (ISMN) in the Prevention of Variceal Rebleeding: Comparison of Cirrhotic and Noncirrhotic Patients

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Both EVL and drug therapy are effective in the prevention of variceal rebleeding. Comparisons between the two modalities are few, and only in cirrhotics. This prospective randomized controlled trial compared EVL with drug therapy (propranolol + ISMN) in the prevention of rebleeds from esophageal varices in cirrhotic and noncirrhotic portal hypertension (NCPH) patients. One hundred thirty-seven variceal bleeders were randomized to EVL (Group I; $n = 71$) or drug therapy (Group II; $n = 66$). In Group I, EVL was done every 2 weeks till obliteration of varices. In Group II, propranolol (dose sufficient to reduce heart rate to 55 bpm/maximum tolerated dose) and ISMN (incremental dose up to 20 mg BD) were administered. Group I and II patients had comparable baseline characteristics, follow-up (12.4 vs. 11.1 months), cirrhotics and noncirrhotics [50(70.4%) and 21(29.6%) vs. 51(77.3%) and 15(22.7%)] and frequency of Child's A (35 vs. 27), B (26 vs. 28), and C (9 vs. 11). The mean daily dose was 109 ± 46 mg propranolol and 34 ± 11 mg ISMN and was comparable in cirrhotic and NCPH patients. Upper GI bleeds occurred in 10 patients in Group I (5 from esophageal varices) and in 18 patients in Group II (15 from esophageal varices) ($P = 0.06$). The actuarial probability of rebleeding from esophageal varices at 24 months was 22% in Group I and 37% in Group II ($P = 0.02$). The probability of bleed was significantly higher in Child's C compared to Child's A/B cirrhotics ($P = 0.02$). On subgroup analysis, in NCPH patients, the actuarial probability of bleed at 24 months was significantly lower in Group I compared to Group II (25% vs 37%; $P = 0.01$). In cirrhotics, there was no difference in the probability of rebleeding between patients in Group I and those in Group II ($P = 0.74$). In Group II, 25.7% patients had adverse effects of drug therapy and 9% patients had to stop propranolol due to serious adverse effects, none required stopping ISMN. There were 10 deaths, 6 in Group I (bleed related, 1) and 4 in Group II (bleed related, 1); the actuarial probability of survival was comparable ($P = 0.39$). EVL and combination therapy are equally effective in the prevention of variceal rebleeding in cirrhotic patients. EVL is more effective than drug therapy in the prevention of rebleeds in patients with NCPH and, hence, recommended. However, in view of the small number of NCPH patients, further studies are needed before this can be stated conclusively.

KEY WORDS: band ligation; β-blockers; isosorbide mononitrate + nadolol (ISMN); secondary prophylaxis; variceal bleeding.

Manuscript received August 27, 2004; accepted December 8, 2004.

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Portal hypertensive patients who experience a bleeding episode from esophageal varices are at a high risk of rebleeding, which may be as high as 70% (1). Such bleeds are associated with a very high mortality rate (1). Hence, prevention of variceal rebleeding is desirable and efforts to improve the current therapeutic protocols are ongoing.

Endoscopic variceal sclerotherapy was initially recommended as the method of choice in secondary prevention as it reduced the frequency of rebleeding and also bleed related mortality in these patients (2). Subsequently, endoscopic variceal ligation (EVL) was found to be equally or more effective in rebleed prevention, with fewer complications (3–7). Band ligation achieves variceal obliteration with fewer endoscopic sessions and also has been found to be effective in controlling active variceal bleeding (3–7).

Reduction of portal pressure and blood flow is a rational approach to prevent bleeding. Drug therapy using nonselective β-blockade has been found to be effective in reducing portal pressure and preventing variceal rebleeding (8). Studies have shown a combination of isosorbide mononitrate and nadolol (ISMN) to be better than sclerotherapy in prevention of variceal rebleeds as well as complications (9). Recent trials have shown medical therapy to be at least as good as EVL in preventing rebleeds. Addition of ISMN to β-blocker has a synergistic effect on decreasing the HVPG (10–12). It has been proposed that ISMN increases the efficacy of propanolol in preventing variceal rebleeds. Two recent trials have compared the combination of a β-blocker and ISMN vs band ligation in the prevention of recurrent variceal bleed, with conflicting results (12, 13). Patch *et al.* (12) reported β-blockers with nitrates to be as effective as EVL in prevention of variceal rebleeding. Lo *et al.* (13), on the other hand, found EVL to be more effective than β-blockers and nitrates in the prevention of rebleed. However, neither of these studies documented any significant difference in survival rate between the treatment groups.

Despite this information, there is no consensus on the most effective mode of therapy for the secondary prevention of rebleed. Furthermore, patients are included in the various clinical trials after careful selection and hence form a select group. Also, patients with noncirrhotic portal hypertension (NCPH), a common cause of portal hypertension in developing countries (14, 15), are excluded. We planned this study with an aim to evaluate the efficacy and safety of combination medical therapy in comparison with endoscopic band ligation in the prevention of recurrent variceal hemorrhage and to assess the survival advantage, if any, with either of these therapies in patients with cirrhotic and NCPH.

PATIENTS AND METHODS

This study was conducted between December 1998 and August 2002. Eight hundred two patients with portal hypertension were seen at the Liver Diseases Follow-up clinic at our hospital during this time interval. Patients presenting to us with hemetemesis and/or melena and proven to have esophageal varices as the bleeding source on upper GI endoscopy were included in the study. Exclusion criteria were as follows: (i) a history of surgery for portal hypertension; (ii) a history of undergoing endoscopic sclerotherapy (EST), EVL, or glue injection before presenting to our hospital; (iii) coexisting hepatocellular carcinoma with cirrhosis of the liver or another malignancy in the body; (iv) severe cardiopulmonary or renal disease; (v) bradycardia (basal heart rate, <5 beats per minute [bpm]) or complete heart block; (vi) a history of severe side effects or contraindications to β-blockers, like bronchial asthma, diabetes mellitus, heart failure, peripheral vascular disease, prostatic hypertrophy, or arterial hypotension (systolic blood pressure [BP], <100 mm Hg); and (vii) refusal to give informed written consent to participate in the trial.

The size of esophageal varices was assessed according to Conn's classification (23): Grade I, visible only during one phase of respiration/performance of valsalva maneuver; Grade II, visible during both phases of respiration; Grade III, 3–6 mm; and Grade IV, >6 mm. The size of the largest varix was assessed by comparison with the shaft of the biopsy forceps (3 mm) or with the distance between the open jaws of the biopsy forceps (6 mm) in the lumen of the lower 2 to 3 cm of the esophagus. Cirrhosis was diagnosed on the basis of clinical, biochemical, histologic, or ultrasonographic evidence. Noncirrhotic portal fibrosis (NCPF) 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 (14, 15). Extrahepatic obstruction of the portal vein was diagnosed when a portal cavernoma was detected by ultrasonography and there were no signs of cirrhosis (14, 15). An effort was made to determine the etiology of liver disease in all patients. Hepatitis B and C virus marker, antinuclear antibody, anti–smooth muscle antibody, serum ceruloplasmin, urinary copper, and serum iron and ferritin assays were performed. History of alcohol abuse was obtained from all patients. The severity of liver disease was assessed by Child–Turcotte–Pugh (CPT) score (25).

Of the 802 patients screened, 208 had presented to us with a history of upper GI bleed (Figure 1). According to the criteria listed previously, 137 patients were considered eligible for the study protocol. Of the 71 patients excluded, 28 had contraindications to β-blockers; the remaining 43 had a history of EVL/EST/glue injection ($n = 14$), prior surgery for portal hypertension ($n = 1$), severe renal or cardiopulmonary disease ($n = 4$), hepatocellular carcinoma or other tumor ($n = 8$), or uncontrolled diabetes mellitus ($n = 10$) or refused to give informed written consent ($n = 6$).

An informed consent was taken from all the patients. The ethical committee of the institution approved the study protocol.

Randomization. Patients were randomized to receive either of the two therapies using a table of random digits (18). Patients were randomized within 24 hr of presentation to the hospital to undergo either EVL or drug therapy. Those presenting with an acute bleed underwent an emergency endoscopy and, if bleeding from esophageal varices was found, underwent band ligation.

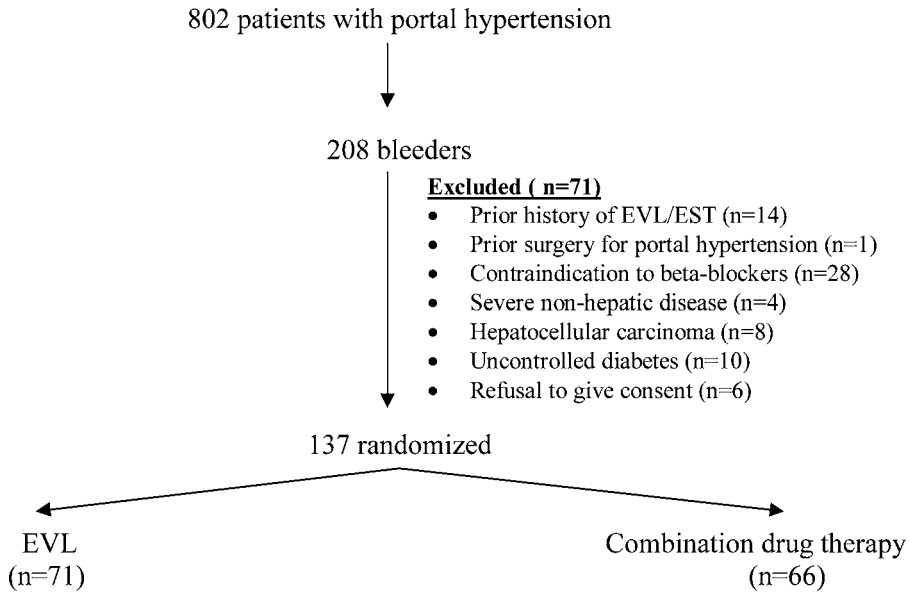


Fig 1. Enrollment of patients included in the study.

Patients were subsequently randomly assigned to either group within the next 24 hr.

Endoscopic Variceal Ligation. Patients assigned to the EVL group underwent ligation at the first endoscopy session or within the next 24 hr. Ligation was done with an endoscope (XV 20; Olympus Optical, Tokyo), using a conventional or a multiband ligator. In each session, as many bands as possible were placed on the varices in the lower 5–7 cm of the esophagus, the number varying from 2 to 10. EVL was done at intervals of 2 weeks till the varices were obliterated or reduced to Grade I size and could not be banded. All side effects including chest pain, dysphagia, fever, and GI bleeding were recorded. Once varices were eradicated, repeat endoscopy was done at monthly intervals for 3 months and then at 3-month intervals to check for recurrent varices.

Patients were routinely advised to have liquids on the day of EVL and subsequently placed on semisolids and solids. They were prescribed 30 mg of lansoprazole once a day and a suspension of sucralfate three or four times per day. Patients with ascites were prescribed oral antibiotics.

Drug Therapy. Patients randomized to the drug therapy arm were screened for any contraindication to β-blockers or ISMN. Those presenting with active variceal bleed underwent emergency EVL. Within 24 hr, these patients were started on propranolol after a baseline electrocardiograph and cardiac evaluation. Treatment was started with propanolol at a dose of 20 mg twice a day. The heart rate and blood pressure were checked after 12 and 24 hr. The dose of propranolol was increased at increments of 20 to 40 mg per day until a 25% decrease in the baseline heart rate was achieved, or the patient achieved a heart rate of 55 bpm, or a maximum dose of 240 mg/day was achieved. The dose was reduced if any of the following occurred: systolic BP $<$90 mm Hg, heart rate $<$5 bpm, or other serious side effects. After attaining a stable dose of propranolol, ISMN was added at a dose of 10 mg twice a day. The dose was escalated at increments of 10–20 mg/day till a maximum dose of 40 mg/day was reached or the patient experienced side effects like headache, dizziness, or hypotension. Patients receiving propranolol were monitored daily until β-blockade was adequate, then monthly for the first 3 months and every 3 months subsequently. Drug compliance was ascertained by interviewing the patient and by measuring the resting heart rate.

End Points. Bleeding from the esophageal varices was the primary end point of the study. Secondary end points included death (due to variceal bleeding, causes related to the underlying liver disease, or unrelated causes), upper GI tract bleeding due to causes not related to the varices, and the development of serious side effects that required the discontinuation of therapy.

Bleeding. Patients presenting with active upper GI bleeding during the study were admitted and subjected to upper GI endoscopy within 12 hr to determine the source of bleeding. Upper GI bleeding was diagnosed and classified using BAVENO III criteria (17). Bleeding from esophageal varices was diagnosed if active bleeding, a "white nipple," or a clot was seen at endoscopy or if there was blood in the stomach in a patient with an esophageal varix and no other potential bleeding source. Bleeding was attributed to portal hypertensive gastropathy if distinct lesions of the gastric mucosa were present and there was endoscopic evidence of an active bleeding lesion, assessed after washing or removal of clots, and there was no evidence of bleeding from esophageal, gastric, or ectopic varices (17). Gastric variceal bleed was diagnosed if active bleeding or a clot was seen on gastric varices 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 (16). Esophageal ulcer bleed as a result of band ligation was diagnosed if there was active bleeding from the ulcer at the site of banding or if there was an adherent clot on the esophageal ulcer with absence of any other potentially bleeding lesions in the upper GI endoscopy (17). Bleeding was categorized as clinically significant when the heart rate was $>$100 bpm at time 0, the systolic BP was $<$100 mm Hg, or there was a postural change $>$20 mm Hg and transfusion requirement of more than 2 U of blood in 24 hr (17).

Patients who had bleed after either EVL or drug therapy were admitted to the hospital and started on vasoactive drugs (terlipressin or somatostatin) immediately. A repeat session of EVL was performed in these patients irrespective of their treatment protocol. The vasoactive drugs were continued for 5 days.

Sample Size Calculation. This study was designed to compare the risks of variceal rebleed as calculated by Kaplan–Meier curves for propranolol and ISMN vs EVL. The probability of rebleed on propranolol and ISMN combination was assumed to be 50% at 2 years. It was hypothesized that EVL would reduce the risk to 25%. Using a two-tailed test with an α value of 0.05 and power $(1 - \beta)$ of 0.80, the required sample size would be 120, i.e., 60 in each group.

Statistical Analysis. Data were analyzed according to intention-to-treat strategy. Quantitative data were expressed as mean (±SD) or median and analyzed using Student's two-tailed t-test or Mann–Whitney test. Qualitative data were analyzed by chi-square test or Fisher 's exact test (18). The actuarial probabilities of bleeding from varices and of death from bleeding or any cause related to liver disease were calculated for all patients by the Kaplan–Meier method, and comparisons were made using the log-rank test. Subgroup analysis was done for cirrhotic and noncirrhotic patients with portal hypertension separately. Cox regression analysis was performed to assess the variables predicting the incidence of bleed. Statistical analysis was done using the SPSS 10.0.5 software package.

RESULTS

A total of 137 eligible patients with portal hypertension and variceal bleed were enrolled in the study. Patients were randomized at entry to either of the two groups: EVL (71 patients) and drug therapy (β-blocker + ISMN [66 patients]). Patients presenting with acute variceal bleed ($n = 21$) underwent emergency EVL to control the bleeding. The numbers of patients presenting as acute bleeding were similar in both groups (11 vs. 10, Table 1). Most of the patients (80 of the remaining 116) had their last bleeding episode within 10 days of admission and recruitment. The median time to bleed in the remaining 36 patients was 4 weeks (range, 2–52 weeks).

The baseline characteristics of the patients are listed in Table 1. There were no differences in the demographic profiles of the patients. The mean follow-up of the patients was 12.4 ± 9.7 months in the EVL and 11.1 ± 7.9 in the drug therapy group (range, 1–40 months), with no difference in either of the two groups. Of those randomized to EVL, a median of 3 banding sessions (range, 1–11) was required to achieve eradication. The median time to eradication was 10 weeks (range, 4–30).

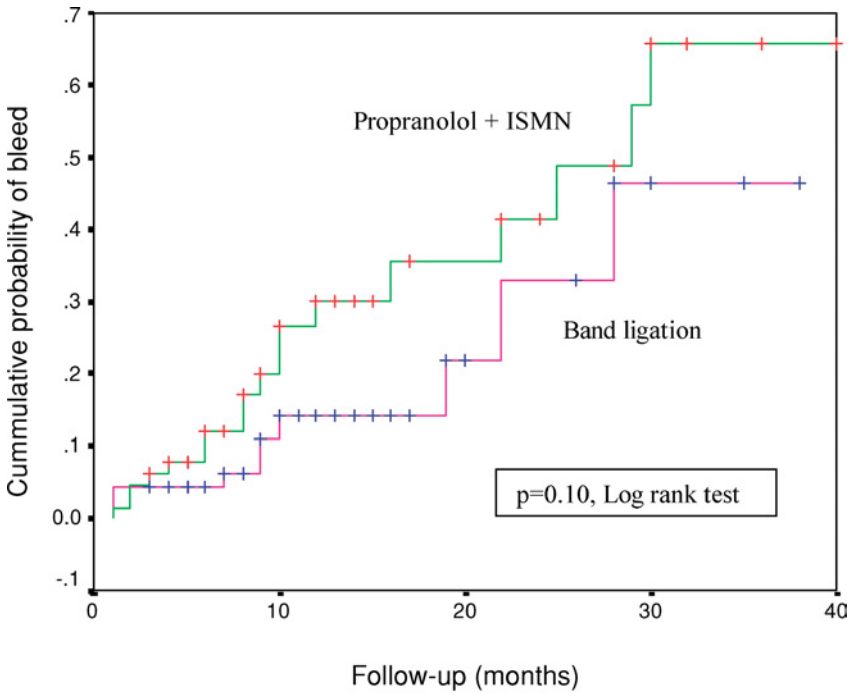
The mean dose of β-blocker achieved for patients in the drug therapy group was 109 ± 46.4 mg/day. The mean ISMN dose was 34.2 ± 11.7 mg/day. Basal resting heart rate before β-blockade was 83.4 ± 10.3 bpm. The baseline heart rate after adequate β-blockade was reduced to 63 ± 6.1 bpm, the mean reduction in heart rate being 24% of baseline.

TABLE 1. BASELINE PATIENT CHARACTERISTICS

Patient characteristic	*Band ligation*	*β-Blocker + ISMN*
Number of patients (n)	71	66
Age (mean yr ± SD)	35.8 ± 17.2	36.2 ± 16
Sex		
Male	51(71)	45(68)
Female	20(28)	21(32)
Etiology		
Cirrhosis—alcoholic	18(25)	15(23)
Hepatitis B	17(24)	15(23)
Hepatitis C	8(11)	8(12)
Wilson's	1(1.4)	0
Autoimmune	1(1.4)	1(1.5)
Budd–Chiari syndrome	2(2.8)	0
PBC	0	1(1.5)
Cryptogenic	6(8.4)	6(9)
Noncirrhotic		
EHPVO	15(21)	13(20)
NCPF	5(7)	3(4.5)
CTP (overall), mean	6.9 ± 2	7.2 ± 1.9
A	35(50)	27(41)
B	26(36)	28(42)
C	10(14)	11(17)
CTP (cirrhosis), mean	7.8 ± 1.8	7.7 ± 1.9
A	16(31)	14(28)
B	25(49)	25(50)
C	10(20)	11(22)
Presenting as acute bleed	11(15)	10(15)
Grade of varices		
II	15(21)	17(26)
III	40(56)	31(47)
IV	16(23)	18(27)
Red color signs	37(52)	27(41)
Gastric varices		
Before eradication	38(53.5)	31(46.9)
After eradication	33(46.5)	31(46.9)
PHG		
Before eradication	24(33.8)	32(48.5)
After eradication	32(45.1)	33(50)
Albumin (g/dl)	3.5 ± 0.5	3.5 ± 0.5
Ascites	24(34)	21(32)
Encephalopathy	6(8)	4(6)
Abnormal PT	28(40)	29(44)
Follow-up (mo)	12.4 ± 9.7	11.1 ± 7.9

Note. Figures in parentheses demonstrate percentages. PBC, primary biliary cirrhosis; EHPVO, extrahepatic portal vein obstruction; NCPF, noncirrhotic portal fibrosis; CTP, Child–Turcotte–Pugh score; PHG, portal hypertensive gastropathy; PT, prothrombin time.

Rebleeding. In the drug therapy arm, 18 patients (27.2%) rebled, compared to 10 patients (14.1%) in the EVL arm ($P = 0.06$) during the study period. The actuarial probability of bleed at the end of 24 and 36 months was 42% and 66%, respectively, in the drug therapy arm, compared to 33% and 47% in the EVL arm ($P = 0.10$, log rank test) (Figure 2). Of the 10 bleeds in the EVL arm, 2 were from gastric varices, 3 were from portal hypertensive gastropathy, 3 were due to post-EVL ulcers, and in another 2 patients the bleeding occurred prior to variceal obliteration and was ascribed to esophageal varices. In the drug



No of patients at risk

Drugs	66	47	24	13	10	8	4	2
Band ligation	71	54	29	16	7	5	3	2

Fig 2. Kaplan–Meier plot showing the actuarial probability of upper gastrointestinal bleed in patients on band ligation or propranolol plus ISMN ($P = 0.10$).

therapy group, 2 patients bled from gastric varices, 1 from portal hypertensive gastropathy, and in the remaining 15, the bleeds were from esophageal varices. When rebleeding from esophageal varices was considered, 15 patients (22.7%) on drug therapy and 5 patients (7%) on EVL rebled. The actuarial probability to rebleed from esophageal varices was significantly higher in the drug therapy group ($P = 0.02$, log rank test) (Figure 3).

To assess the influence of etiology of portal hypertension, patients with cirrhosis and NCPH were separately analyzed in the two treatment arms. On subgroup analysis, when only cirrhotics were compared, 9 (12.7%) patients in the EVL arm had bled, compared to 12 (23.5%) patients in the drug therapy arm, the actuarial probability of bleed at 24 months being 37% in the EVL arm and 46% in the drug therapy arm ($P = 0.74$, log rank test). When only noncirrhotic patients were compared, the bleed rate was significantly higher in the drug therapy arm. Only 1 of 21 (4.7%) in the EVL arm and 6 of 15 patients (40%) in the drug therapy arm bled. The actuarial probability to bleed at 24 months was 25% in the EVL arm and 37% in the drug therapy arm ($P = 0.01$, log rank test) (Figure 4).

When bleed rates in these patients were compared according to Child's status, there were 13 (20.9%) bleeds in Child's A, 8 (14.3%) in Child's B, and 7 (36.8%) in Child's C patients. The actuarial probability to bleed at 24 months was significantly higher in Child's C compared to Child's A and B patients ($P = 0.02$, log rank test) (Figure 5).

A detailed analysis was undertaken to assess the factors that could predict rebleed. Factors analyzed included age, sex, etiology of liver disease, Child's status, grade of varices, red signs, presence of gastric varices, portal gastropathy, and dose of propranolol and ISMN. On univariate analysis, sex, Child's status, presence of red signs, and ISMN dose were found to significantly predict rebleeding (Table 2). On multivariate analysis, age (relative hazard [RH], 1.03; 95% CI, 1.00–1.06; $P = 0.03$), sex (RH, 2.51 [1.16–5.41]; $P = 0.02$), and Child's status (RH, 1.57 [0.58–4.26]; $P = 0.05$) significantly predicted rebleeding. On adjusting age and sex as confounding factors, Child's status was the only factor that predicted rebleeding (Table 2).

Survival. Ten patients died during the follow-up period, 6 in the EVL arm and 4 in the drug therapy arm.

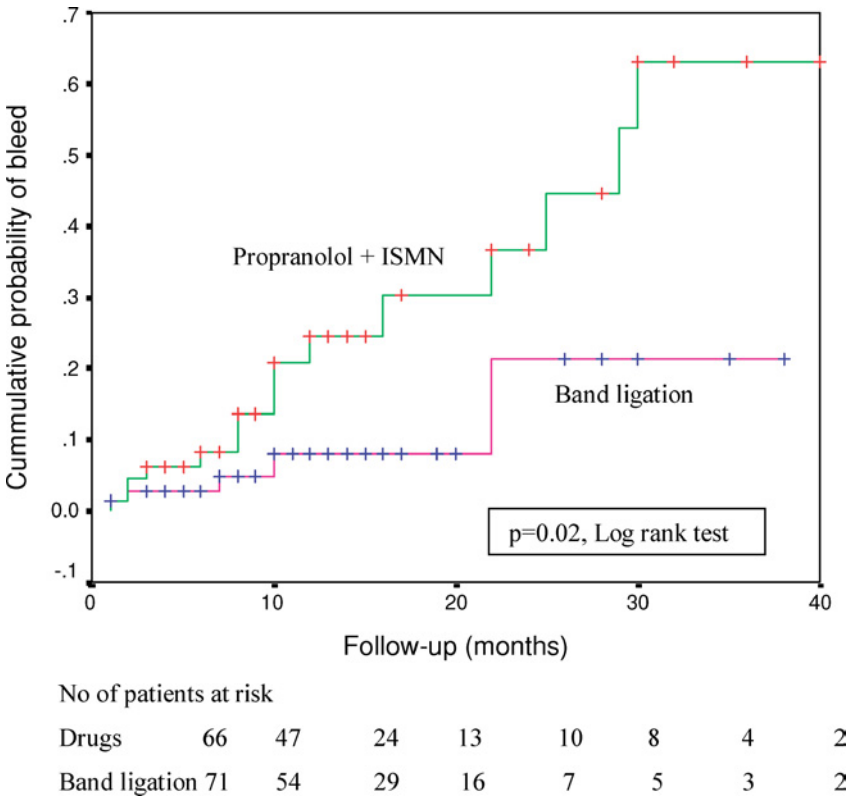


Fig 3. Kaplan–Meier plot showing the actuarial probability of bleed from esophageal varices in patients on band ligation or propranolol plus ISMN ($P = 0.02$).

There was one bleed-related death in the EVL group and one in the drug therapy group. Other deaths were due to complications of end-stage liver disease (hepatorenal syndrome, 4; liver failure, 2; hepatic encephalopathy, 2). Kaplan–Meier estimate revealed no significant difference in the survival rates between the two treatment groups ($P = 0.39$, log rank test) (Figure 6).

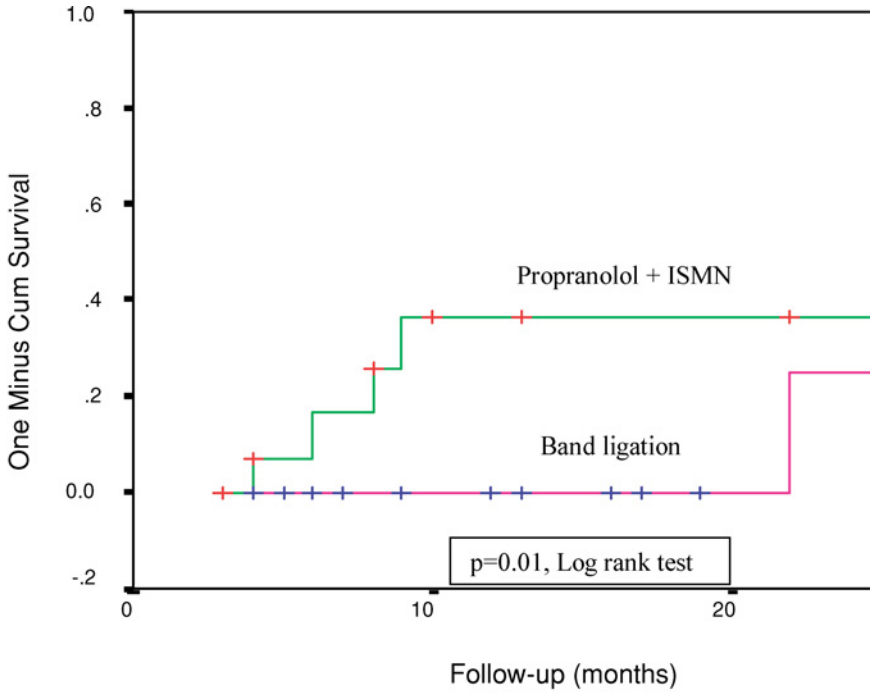
Adverse Effects. Patients in the EVL arm experienced minor side effects. Transient dysphagia, chest discomfort, and fever were observed in 24 (33.8%) patients. These resolved in all of the patients within the next 2–4 weeks. None of the patients developed esophageal strictures. Four episodes of bleeding were documented from post-EVL ulcerations in these patients. These patients were admitted and managed by blood transfusions, correction of coagulation profile with FFP, albumin, parenteral antibiotics, and repeat endoscopic procedure and band ligation. None of these patients died.

Six patients on propranolol experienced side effects serious enough to merit withdrawal of therapy. Two of them had hypotension on the initial dose of propranolol, and another two had severe breathlessness. Two patients had severe headache. Dose adjustments were required in five patients but propranolol could be continued in them. No serious adverse effects to ISMN requiring discontinuation were encountered. Six patients had minor headache, which resolved either with time or on decreasing the dose of ISMN. The overall complication rate in the drug therapy arm was 25.7% (17 of 66 patients).

DISCUSSION

Variceal rebleeding in portal hypertension can be theoretically decreased either by decreasing the portal pressure (by medical therapy [β-blockade $\pm$ ISMN], transjugular intrahepatic portosystemic shunting, or shunt surgery) or by obliterating the varices by local therapy such as band ligation.

Our trial compared the efficacy of variceal obliteration using EVL with reduction in portal pressure by pharmacotherapy with propranolol plus ISMN combination in prevention of rebleeding from esophageal varices. The actuarial probability to rebleed was similar in the EVL and drug therapy groups in cirrhotic patients (37% and 46%, respectively). The results of the present prospective study clearly demonstrate that drug therapy is as effective as band ligation in preventing rebleed from esophageal varices in cirrhotic patients. Our results are comparable to



No of patients at risk						
Drugs	15	10	5	4	4	2
Band ligation	21	16	11	8	4	3

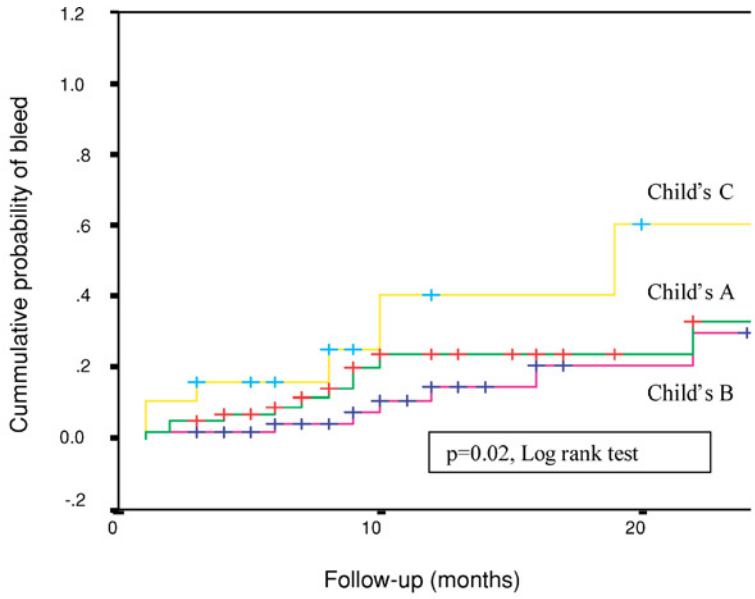
Fig 4. Kaplan–Meier plot showing the actuarial probability of bleed in patients with NCPH on band ligation or propranolol plus ISMN ($P = 0.01$).

those reported by Patch *et al.* (12) and Lo *et al.* (13). The rebleed rate at 1 year in the study by Patch *et al.* (12) was 43% on drug therapy and 53% on EVL. There was no significant difference in the probability to bleed between the two groups. In a similar trial by Lo *et al.* (13), the upper GI bleeding from all sources was similar in the two groups, but the EVL group showed a significantly lower rate of bleeding from esophageal varices. The actuarial probability of rebleed at 30 months in their study was 48% in the EVL group, compared to 70% in the drug therapy group.

Our study is, however, novel, as the patient population consisted of both cirrhotic and NCPH patients (cirrhotic, $n = 101$; NCPH, $n = 36$). This is especially relevant, as a significant proportion of patients in third world countries have NCPH (15).

A significant observation in our study is the higher bleed rate on drug therapy compared to band ligation in patients with NCPH. To our knowledge, there have been no previous trials comparing these modes of treatment in preventing rebleeds in patients with NCPH. There are limited data on the efficacy of pharmacotherapy in patients with NCPH. The only controlled trial of β-blockers in NCPH patients was published by Kiire *et al.* (19). This study reported a 1-year rebleed rate of 20% on propranolol, compared to 80% on placebo. However, the patient population in this study was different, as most of the patients in this study had schistosomiasis as a cause of NCPH. There are anecdotal case reports of a response to propranolol in NCPH patients (20). Nonselective β-blockers inhibit both β-1 and β-2 adrenergic receptors. These agents lower portal pressure by decreasing cardiac output via β-1 receptor blockade. In addition, β-2 receptor blockade leads to unopposed α-adrenergic activity, resulting in splanchnic vasoconstriction and, hence, reduced portal pressure. The low response rate to β-blockers in NCPH could be because the site of resistance in these patients is presinusoidal. We have shown in this study that EVL is more effective than β-blockers in prevention of rebleed in noncirrhotic patients. However, in view of the small number of noncirrhotic patients in our study, trials with a higher number of NCPH patients are needed for conclusive evidence. This study should act as a basis for such trials to follow.

In the band ligation group, with a median of three sessions, variceal obliteration was achieved. The time to



No of patients at risk						
Child's A	62	43	21	13	7	5
Child's B	56	45	26	14	9	7
Child's C	19	11	4	3	1	1

Fig 5. Kaplan–Meier plot showing the actuarial probability of bleeding according to the Child's status of the patients ($P = 0.02$).

achieve variceal obliteration was 10 weeks, a little higher in the present study compared to the previous study published from our center (24). This is because we carried out ligation at 2-week intervals in the present study, compared to once-a-week banding in the previous study. Moreover, the banding was postponed by 2 weeks in the presence of active ulceration in the present study.

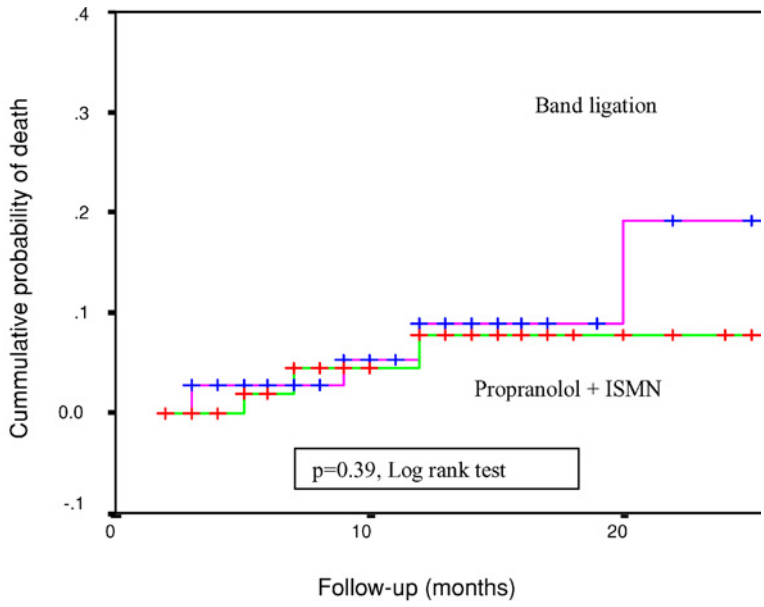
The mean dose of β-blocker (109 mg) administered in our study was higher than that used by Patch *et al.* (12) (80 mg) and similar to that described previously (21). The mean drop in heart rate after the maximum tolerated dose was 24% (83 to 63 bpm) in our study. This compares well with the recommended reduction in heart rate to achieve a significant reduction in variceal bleeding. The mean ISMN dose of 34 mg is also in concordance with that used in the previous studies (12, 13).

TABLE 2. FACTORS ASSOCIATED WITH REBLEEDING

	Relative hazard	*95% CI*	P
Univariate analysis			
Age	1.02	0.99–1.04	0.16
Sex	2.30	1.03–5.14	0.04
Etiology	1.73	0.68–4.35	0.22
Child's status	2.49	0.91–6.84	0.05
Red signs	2.96	1.28–6.82	0.01
Gastric varices	0.81	0.37–1.79	0.61
Propranolol dose	1.00	0.99–1.01	0.74
ISMN dose	0.94	0.89–0.99	0.01
Multivariate analysis			
Age	1.03	1.00–1.06	0.03
Sex	2.51	1.16–5.41	0.02
Child's status	1.57	0.58–4.26	0.05

In the EVL group, there were three bleeds due to EVL-induced ulcerations. None of these patients died due to bleed. Other complications seen in the EVL group were transient retrosternal pain and fever that subsided without any specific therapy. No esophageal strictures were seen. Six patients had serious adverse effects to propranolol requiring discontinuation. No serious adverse effects to ISMN requiring discontinuation were encountered. The overall complication rate in the drug therapy group was 25.7% (17 patients). This is similar to the 20–25% incidence reported in the previous trials (12, 13, 22).

Survival was not different between the patients treated by the two therapeutic approaches in our study. Two previous studies have shown a better survival in patients on drug therapy compared to those on EVL (10, 13). On the other hand, in the study published by Patch *et al.* (12), there was no significant difference in survival between the two groups. The actuarial probability of survival in our study is higher than that published in these trials. This



No of patients at risk

Drugs	66	49	30	19	13	9
Band ligation	71	55	28	16	9	6

Fig 6. Kaplan–Meier plot showing the actuarial probability of survival in patients on band ligation or propranolol plus ISMN ($P = 0.39$).

may be due in part to the proportion of NCPH patients in our study who have near-normal hepatic parenchymal function and hence a lower mortality rate than cirrhotic patients. Nearly 54% of patients in the present study were Child's B and C, compared to 89% in the study by Patch *et al.* and 78% in the study by Lo *et al.* This could also have contributed to the lower mortality rate in our study.

The probability of rebleed was higher in Child's C compared to Child's A and B cirrhotic patients ($P = 0.02$). Factors found to be associated with increased risk of rebleed were age, sex, Child's status, presence of red signs, and lower ISMN dose. On multivariate analysis, age, sex, and Child's status emerged as predictors of rebleed. On adjusting age and sex as a confounding factor, only Child's status could significantly predict the incidence of rebleed. This is in agreement with the fact that with increased severity of liver disease, the risk of bleeding increases (26, 27).

In conclusion, EVL and a combination of drugs are equally effective in the prevention of variceal rebleeding in cirrhotic patients. EVL is more effective than drug therapy in prevention of rebleeds in patients with NCPH. Band ligation may be considered the treatment of choice for prevention of rebleeds from esophageal varices in patients with NCPH. However, this needs to be validated in a prospective randomized controlled trial with a higher number of NCPH patients. There is no survival advantage of one treatment over the other. It remains to be seen whether combining ligation with pharmacotherapy could have additional benefits for patients who have bled in the past.

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