Prophylaxis of First Hemorrhage from Esophageal Varices by Sclerotherapy, Propranolol or Both in Cirrhotic Patients: A Randomized Multicenter Trial

THE PROVA STUDY GROUP

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The objective of this randomized multicenter trial was to assess the prophylactic effect on the incidence and severity of the first variceal hemorrhage of endoscopic sclerotherapy, propranolol and the combination of the two compared with none of these treatments in patients with cirrhosis and esophageal varices. Among 819 cirrhotic patients who never had experienced variceal bleeding, esophagoscopy revealed varices in 379, of whom 286 were enrolled in the trial; 73 were allocated to sclerotherapy (paravenous polidocanol [10 mg/ml] every 1 to 2 wk until eradication), 68 to propranolol (slow-release preparation in one daily dose adjusted to provide about 25% heart rate reduction), 73 to both treatments and 72 to neither of the two treatments. The patients were observed for up to 42 mo, with an average of 15 mo. After variceal bleeding, patients in all groups received sclerotherapy only. The incidences of variceal bleeding (n = 50) were almost identical in the four groups. The relative risk (with 95% confidence limits) with sclerotherapy was 1.06 (0.61 to 1.84), and the relative risk with propranolol was 0.92 (0.53 to 1.60). The mortality rate after variceal bleeding (n = 29) did not differ significantly either. The mortality rate without variceal bleeding (n = 46) was 2.75 (1.45 to 5.22) times higher in the sclerotherapy groups than in the nonsclerotherapy groups (p = 0.002), whereas propranolol showed no effect, the relative risk being 1.17 (0.66 to 2.10). The total mortality rate showed no significant difference between the sclerotherapy, propranolol and control groups, but the combined therapy group had a significantly increased mortality rate.

This trial yielded evidence against prophylaxis of variceal hemorrhage in cirrhosis by endoscopic sclerosing injections, with or without propranolol, and no support of propranolol used alone. (HEPATOLOGY 1991; 14:000-000.)

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In cirrhotic patients the mortality rate within 6 wk of the first episode of variceal hemorrhage is approximately 50%, and only 30% of the patients are alive 3 yr later (1, 2). Both endoscopic sclerotherapy and treatment with β-adrenergic-receptor blockers such as propranolol can reduce the risk of recurrent bleeding after the first hemorrhage, and long-term survival may improve also (3, 4). A comparison of sclerotherapy and β-blockers suggests that the effects are about equal (3), whereas trials assessing the combination of propranolol and sclerotherapy vs. either sclerotherapy alone or propranolol alone have given discrepant results (5-10).

Despite the gains by the two treatments, the overall results have remained disappointing. Several trials

TABLE 1. Patient characteristics (mean values or percentages) at randomization[a]

Characteristics	Treatment group			
	Control n = 72	Sclerotherapy n = 73	Propranolol n = 68	Combined n = 73
Clinical				
Age (yr)	54	55	53	55
Men (%)	74	75	56	74
Alcoholic cirrhosis (%)	87	82	78	81
Current alcohol intake (gm/day)	19	17	17	13
Need daily support (%)	6	8	3	6
Encephalopathy (%)[b]	14	4	4	10
Ascites (moderate or tense) (%)[b]	41	29	31	34
Underweight (%)	23	18	7	17
Resting heart rate (per min)	84	82	83	84
Systolic blood pressure (mm Hg)	128	129	134	130
Diastolic blood pressure (mm Hg)	75	76	79	77
Variceal[c]				
Size, grade 1 (%)	39	47	40	40
grade 2 (%)	49	36	47	46
grade 3 (%)	12	18	13	14
Number of columns	2.6	2.6	2.5	2.7
Maximum length (cm)	11	11	11	11
Blue color (%)	62	66	69	78
Gastric varices (%)	3	10	12	7
Blood chemistry				
Hemoglobin (mmol/L) (7.1-10.9)[d]	7.9	7.9	8.2	7.8
Thrombocyte count (10^9/L) (150-350)	165	175	169	151
Bilirubin (μmol/L) (2-17)	44	35	34	40
AST (IU/L) (10-40)	64	67	69	73
Alkaline phosphatases (IU/L) (50-275)	381	466	388	364
Clotting factors 2, 7, 10 (arbitrary) (70-130)	68	69	72	61
Albumin (μmol/L) (540-800)	487	513	513	499
Creatinine (μmol/L) (49-121)	100	92	84	92

[a]The information was missing for seven items in patients 1-9, for eight items in patients 10-19 and for two items in patients 20-29 (alcohol intake and thrombocyte count).

[b]Within the last 3 mo.

[c]At the screening endoscopy, the varices were characterized by size as maximum degree of protuberance (grade 1 = less that the radius of the varix [sessile]; grade 2 = about the radius; grade 3 = more than the radius [pedunculate]; number of columns at the gastroesophageal junction; maximum length; color (like the mucosa or blue); and presence of gastric varices.

[d]Reference intervals.

therefore have evaluated the prophylactic effects of endoscopic sclerotherapy (11-24) and of β-receptor blockers (25-29). However, the trials have been undertaken in various selected patient populations, and the results have been ambiguous (3, 4). None of the published trials have combined the two modalities for primary prophylaxis.

We have conducted a large randomized trial of the prophylactic effect on the incidence and severity of the first variceal hemorrhage of sclerotherapy, of propranolol, and of the combination of the two compared with none of these treatments in patients with cirrhosis and esophageal varices.

PATIENTS AND METHODS

Trial Enrollment

Screening Endoscopy of the Recruitment Population. All patients with biopsy-proven cirrhosis (or clinically evident cirrhosis when a biopsy was contraindicated) who never had experienced transfusion-requiring upper gastrointestinal bleeding ascribed to esophageal varices and who were living in the referral area of the hospitals were offered upper gastrointestinal endoscopy for assessment of esophageal varices as previously defined (30).

Trial Enrollment Criteria. The patients had to meet all the following criteria before randomization: (a) presence of esophageal varices, (b) no previous sclerotherapy of esophageal varices, (c) no current β-blocking treatment or, if so, only if it could be discontinued or replaced by another medication, (d) repeated sclerotherapy technically feasible, and (e) permanent β-blocking treatment feasible (i.e., the patient had to be able to administer the medication, and none of the standard contraindications of β-adrenergic blockade should have been present). Before randomization, a series of clinical, endoscopic and biochemical characteristics were recorded (Table 1).

Randomization. As soon as possible after the screening endoscopy the patients were equally allocated to four treatment groups. The *control group* had no sclerotherapy and no propranolol; the *sclerotherapy group* had sclerotherapy but no propranolol; the *propranolol group* had propranolol but no

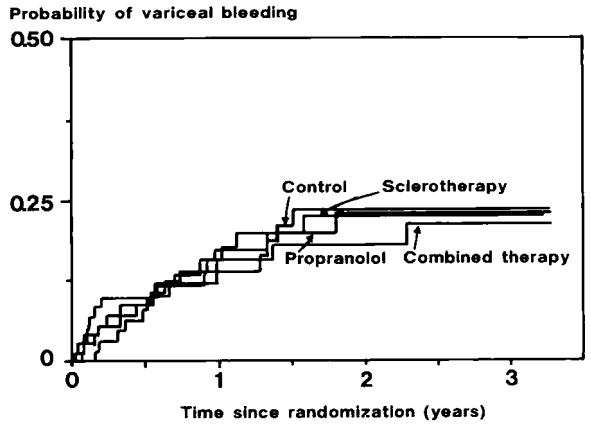

FIG. 1. Cumulative probability of transfusion-requiring variceal bleeding in the four treatment groups. This probability is the estimate of the proportion of patients who from entry through a defined point in time will experience this bleeding.

sclerotherapy; and the *combined therapy group* had both treatments.

If any of the treatments for clinical or practical reasons could not begin immediately after screening endoscopy, randomization was postponed. The randomization was generated from tables of random numbers, stratified by participating hospitals and administered by sealed, opaque and consecutively numbered envelopes. No placebo medication and no sham endoscopy were used.

Treatment

Sclerotherapy. Sclerotherapy was performed with flexible endoscopes after sedation by 5 to 10 mg of diazepam given intravenously. At each session, 10 mg/ml of polidocanol (Aetoxysclerol, Kreussler, Inc., Germany) was injected paravenously into the submucosa in deposits of 1 to 2 ml within 2- to 3-cm intervals beginning at the gastroesophageal junction, with a maximum of 30 ml/session. The treatment was repeated within 1- to 2-wk intervals until the varices were eradicated. Follow-up endoscopy was performed every 3 mo during the first year and every 6 mo the following years. In case of recurrence, a similar series of sclerosing injections was undertaken.

Propranolol Treatment. Propranolol treatment was given orally as a slow-release preparation (Inderal Long-acting, ICI Pharmaceuticals Inc., UK) once daily. The starting dose was 160 mg, and during the first 2 wk the dose was adjusted in units of 80 mg with the aim of reducing the heart rate by approximately 25%. However, the daily dose was not allowed to exceed 400 mg. The resting heart rate was to be kept above 50 beats/min and the systolic blood pressure was to stay above 90 mm Hg.

Follow-up

All patients were to be seen every 3 mo even if the treatment was discontinued or the strategy was violated.

End-points. End-points were defined as either death or transfusion-requiring upper gastrointestinal hemorrhage, of which esophageal varices were judged to be the most likely source. If possible, the bleeding source was confirmed by emergency endoscopy (actively bleeding varix, a clot on a varix or no other possible sources than varices). After the first variceal hemorrhage propranolol was discontinued, and the patient was treated routinely by sclerosing injections. Clinical follow-up continued for 6 wk after the first transfusion-requiring variceal bleeding, and follow-up regarding the mortality rate continued until the end of the trial.

Hemorrhages Not Considered as End-points. Any episode of upper gastrointestinal hemorrhage that occurred was recorded by date, likely source and number of blood transfusions given. Hemorrhages judged as originating from injuries caused by sclerotherapy within 24 hr and variceal hemorrhages not requiring blood transfusions were recorded but not considered as end-points stopping the trial protocol.

Stopping Rules

Recruitment of patients for the trial continued for a maximum of 3 yr unless the steering committee decided otherwise. We estimated that 440 patients were necessary if interaction was allowed for between treatment effects, and 220 patients if no interaction was allowed for (assuming an annual rate of variceal bleeding of 25%, a 50% reduction in this rate by prophylaxis, a minimum of 1 yr of follow-up, a type I error of 0.05 and a type II error of 0.20).

Ethical Considerations

The trial protocol adhered to the Helsinki Declaration II and was approved by the official ethical committee for Copenhagen. Informed consent was obtained.

Statistical Analysis

All analyses of the effects of the treatment regimens were carried out using the intention-to-treat principle (31), which implied that the analyses included all randomized patients throughout the available follow-up period irrespective of treatment received.

The failure-time data were analyzed using a competing risks model (32, 33). The competing end-points were transfusion-requiring variceal bleeding and death without such bleeding. The cumulative probabilities of the occurrence over time of the two end-points were estimated from the cause-specific failure rates (34). Comparison of the failure rates in the four treatment groups was performed by the log-rank test with and without stratification by single patient characteristics of possible prognostic value (31, 35). The effect of each of these characteristics was evaluated by the log-rank test with test for trend when considered appropriate (31, 35). The proportional hazards regression model (Cox regression model) (32, 36) was used to estimate and test treatment effects and possible interaction between them (i.e., if the effect of one treatment depended on whether the patient was allocated to the other treatment). The simultaneous effects of treatment and individual patient characteristics were also evaluated by the proportional hazards regression model. Differences between the four treatment groups in the mortality rate after the occurrence of transfusion-requiring variceal bleeding were analyzed by the Fisher exact test.

RESULTS

The trial began in November 1985. After 3 yr, a preliminary statistical analysis, ready in March 1989, suggested a harmful effect of sclerotherapy and no detectable effect of propranolol; therefore the trial was stopped.

Characteristics of the Patient Population

A total of 819 screening endoscopies were carried out, and varices were found in 379 (46%) patients of whom 286 (75%) were enrolled in the trial. The reasons for excluding the remaining 81 patients were as follows: 38 refused to participate; 13 patients presented contraindications to propranolol; 12 were not included because they died shortly after the endoscopy; 10 participated in other trials; 9 were unable to provide informed consent; 4 had advanced malignancies; 3 patients did not accept liver biopsy for confirmation of the clinical suspicion of cirrhosis; 2 had severe coagulopathy; 1 was accepted for liver transplantation; and 1 was pregnant.

The randomization resulted in the allocation of 72 patients to the control group, 73 to the sclerotherapy group, 68 to the propranolol group and 73 to the combined therapy group. In each of the seven half-year periods of the trial, 52, 55, 38, 39, 37, 35 and 30 patients were enrolled. Eleven hospitals contributed with 65, 56, 30, 29, 27, 26, 17, 14, 11, 6 and 5 patients, respectively. The two hospitals with the lowest numbers (Rikshospitalet in Oslo and Rigshopsitalet in Copenhagen) were affiliated with the project at a late stage.

The randomization produced fairly similar groups (Table 1). The most marked deviations were in sex distribution (few men in the propranolol group), encephalopathy (most in the control group), ascites (most in the control group), underweight (most in the control group), variceal size (most grade 2 and fewest grade 1 and 3 in the control group) and variceal color (most with blue varices in the combined therapy group). Although these deviations by definition are random and hence meaningless to assess statistically, they were taken into account in the assessment of the treatment effect using multivariate regression to control for the imbalances of those variables that proved to be of prognostic importance.

TABLE 2. Evaluation of treatment effects by analysis of Cox regression models

End-point[b]	Regression coefficients[c] (S.E.) Sclerotherapy	Propranolol	Combined therapy
Variceal bleeding			
Model A1	0.09 (0.39)	−0.05 (0.40)	−0.03 (0.42)
Model A2	0.06 (0.28)	−0.09 (0.28)	— —
Model B1	0.07 (0.40)	−0.08 (0.39)	−0.03 (0.41)
Model B2	0.06 (0.28)	−0.09 (0.28)	— —
Model C1	0.17 (0.42)	0.23 (0.42)	0.05 (0.42)
Model C2	−0.01 (0.29)	0.05 (0.29)	— —
Death without variceal bleeding			
Model A1	0.62 (0.45)	−0.42 (0.57)	1.01 (0.42)
Model A2	1.01 (0.33)	0.16 (0.30)	— —
Model B1	0.60 (0.45)	−0.45 (0.57)	1.00 (0.42)
Model B2	1.02 (0.33)	0.16 (0.30)	— —
Model C1	1.09 (0.47)	0.08 (0.58)	1.15 (0.43)
Model C2	1.08 (0.34)	0.07 (0.30)	— —

[a]The models were constructed as follows: Models A1 and A2 included only the treatment variables and were based on the actual observation time. Models B1 and B2 included only the treatment variables and were based on the observation time extended until the end of the trial. Models C1 and C2 included treatment variables and those entry variables that had an independent prognostic effect—variceal size and clotting factors for variceal bleeding; sex, bilirubin, and albumin for death without variceal bleeding—and were based on actual observation time. In models A1, B1 and C1 each treatment group is compared with the control group. In models A2, B2, and C2 the two groups allocated to sclerotherapy are compared with those allocated to no sclerotherapy; this is the same for the groups allocated to propranolol and no propranolol (disregarding interaction in treatment effects).

[b]For definition of end-points, see "Patients and Methods."

[c]Relative risk estimates may be obtained by exp(coefficient). Positive coefficients indicate increased risk by the treatment at issue.

Treatment Received and Follow-up

None of the patients in the control group received sclerotherapy or β-adrenergic blockers during the study period.

In the sclerotherapy group all but six patients received sclerosing injections. Three did not want the treatment; before treatment was started, one bled from varices, one had a hepatoma diagnosed and one had Budd-Chiari syndrome diagnosed. Among the 67 treated patients (92%), on average 55 ml polidocanol was used. The varices reduced in size in 52 patients (78% of treated patients), and eradication was achieved in 44 patients (66% of treated patients). The patients underwent endoscopy on the average 7.1 times (range = 1 to 17). One patient was treated by 80 mg propranolol (Inderal) twice daily for arterial hypertension. None of the others received treatment by β-adrenergic blockers during the study period.

In the propranolol group all patients but two (neither wanted treatment) were started on the drug. In four patients, treatment was stopped because of side effects before an adjusted dose was reached. The average adjusted daily dose of the remaining 62 patients (91%) was 146 mg (range = 40 to 320 mg), and at the first 3 mo visit their heart rate was reduced 20% on average. Twelve patients (19% of treated patients) later discontinued medication, seven because of side effects and five because of withdrawal. No patients in the propranolol group received prophylactic sclerotherapy. One patient who reported to have had an episode of hematemesis and melena 2 days before admission was treated by sclerotherapy but did not need blood transfusion.

In the combined therapy group, sclerotherapy was performed in all but three patients. Two did not want the treatment, and one had small varices at the entry endoscopy but no varices at several subsequent endoscopies. The remaining 70 patients (96%) were treated with 57 ml polidocanol on average. The varices reduced in size in 60 patients (86% of treated patients) and were eradicated in 47 patients (67% of treated patients). Endoscopy was performed 7.5 times on average (range = 1 to 22). Two patients did not want to start propranolol treatment, and seven patients discontinued treatment because of side effects before adjustment was reached. In the remaining 64 patients (88%), the average

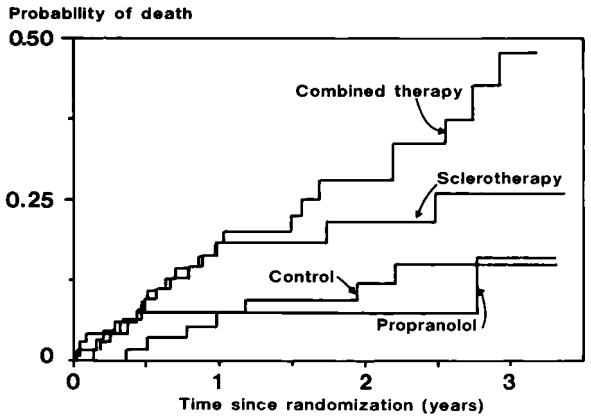

FIG. 2. Cumulative probability of death without transfusion-requiring variceal bleeding in the four treatment groups (see legend of Fig. 1).

dose was 140 mg/day (range = 80 to 320 mg), on which a mean reduction in heart rate of 17% at the first 3-mo visit was obtained. During the study, eight patients (13% of treated patients) discontinued medication, three because of side effects and five because of withdrawal.

Twenty patients (7%) withdrew from the follow-up program before the end of the trial. Of these patients, three (4%) were in the control group, five (7%) were in the sclerotherapy group, seven (10%) were in the propranolol group and five (7%) were in the combined therapy group. The average actual observation time was 15.4 mo (range = 0 to 41.5 mo) in the total group and 16.5 mo, 14.0 mo, 16.5 mo and 14.6 mo in the four treatment groups, respectively. Because six patients considered lost for follow-up later turned up with end-points, two series of analysis were carried out, one with the actual observation time and one with the observation time stopped on April 30, 1989.

Incidence of Variceal Bleeding

Fifty patients (17%) had an episode of transfusion-requiring variceal hemorrhage. Thirteen (18%) were in the control group, 13 (18%) were in the sclerotherapy group, 12 (18%) were in the propranolol group and 12 (16%) were in the combined therapy group.

The variceal source was verified by endoscopy and/or autopsy in all but six patients (two in each treatment group except for the propranolol group), all of whom died within 6 wk (on day 0, 0, 2, 2, 14 and 23).

One patient in the sclerotherapy group had an episode of variceal bleeding immediately after a sclerotherapy session. The episode required one blood transfusion and was not counted as an end-point. Four patients had variceal bleeding that did not require blood transfusion. One patient was in the control group, two patients were in the sclerotherapy group (probably induced by the procedure) and one patient was in the propranolol group. Only the last-mentioned patient later had end-point bleeding as defined earlier.

The cumulative probabilities of transfusion-requiring variceal bleeding over time in the four treatment groups were almost identical (overall log-rank test for bleeding rates, $p = 0.99$) (Fig. 1). They were also almost identical when compared after stratification according to the characteristics listed in Table 1 (stratified log-rank tests, all $p > 0.05$).

Correspondingly, the analysis by the Cox regression model showed no significant treatment effects (Model A1 and A2; Table 2). The relative risk of variceal bleeding in patients receiving sclerotherapy vs. patients receiving no sclerotherapy was 1.06 with 95% confidence intervals of 0.61 through 1.84. Likewise, the relative risk for propranolol vs. no propranolol was 0.92 with confidence intervals of 0.53 through 1.60. Essentially the same results were obtained if the observation period was extended to the end of the trial for those lost to follow-up (Models B1 and B2), and if the variceal size and the clotting factors (which maintained significant, independent prognostic values, data not shown) were included in the regression analysis (Models C1 and C2).

Course after Variceal Bleeding (Table 3)

Fourteen patients (28%) died within 24 hr of the cessation of the first transfusion-requiring variceal bleeding, and no significant differences were seen between treatment groups. The case fatality was lowest in the propranolol group (8%) and highest in the combined therapy group (50%) ($p = 0.1$). At 6 wk, 21 patients (42%) had died, and the case fatality was still lowest in the propranolol group (17%) and highest in the combined therapy group (67%) ($p = 0.05$).

The duration of bleeding, amount of blood transfusion, use of balloon tamponade and frequency of rebleeding did not show treatment group differences corresponding to the pattern of the early mortality rate (Table 3).

Seven patients died after 6 wk. Two were in the control group, three were in the propranolol group and two were in the combined therapy group. The overall mortality rate after variceal bleeding showed no significant reductions compared with the control group.

Death Without Variceal Bleeding

Forty-six patients (16%) died without transfusion-requiring variceal bleeding. Eight (11%) were in the control group, 13 (18%) were in the sclerotherapy group, five (7%) were in the propranolol group and 20 (27%) were in the combined therapy group. The cumulative probabilities of death over time (Fig. 2) were higher in the groups in which sclerotherapy was part of the program and highest in the combined therapy group (overall log-rank test for mortality rates, $p = 0.006$).

According to the analysis by the Cox regression model (Model A1, Table 2), only the combined therapy group differed significantly from the control group. However, the effect of sclerotherapy was not significantly dependent on whether propranolol was given and vice versa. The sclerotherapy groups exhibited a 2.75 times higher risk of dying (95% confidence intervals = 1.45 to 5.22) than the nonsclerotherapy groups, a difference

TABLE 3. Course after first episode of transfusion-requiring variceal bleeding

Treatment group	Patients (n)	Bleeds (n)	Duration (days) (Mean per patient)	Transfusion (pints) (Mean per patient)	Balloon tamponade (bleeds) (n)	Death[a] (n)	Death[a] (% of patients)
First episode							
Control	13	13	4.5	4.2	2	4	31
Sclerotherapy	13	13	3.5	6.1	7	3	23
Propranolol	12	12	5.4	7.9	4	1	8
Combined	12	12	2.2	9.7	7	6	50
Episodes during 6 wk[b]							
Control	13 (4)[c]	17	6.0	6.6	4	6	46
Sclerotherapy	13 (4)[c]	19	7.2	9.5	12	5	38
Propranolol	12 (5)[c]	17	6.5	10.5	6	2	17
Combined	12 (3)[c]	16	3.3	11.5	9	8	67

[a]All death occurring within 24 hr of cessation of the first episode and within 6 wk of the start of the first episode, respectively, are included in these counts.

[b]Includes data pertaining to the first episodes.

[c]Number of patients with more than one episode of variceal bleeding during the 6 wk (recurrent bleeding was defined as bleeding occurring after more than 24 hr of nonhemorrhagic gastric-tube aspiration).

that was highly significant (Model A2; p = 0.002). The propranolol groups showed almost the same risk as the nonpropranolol groups, with a relative risk of 1.17 with confidence limits from 0.66 to 2.10 (p = 0.6). Almost the same results were obtained when the observation periods were extended to the end of the trial for all patients (Models B1 and B2, Table 2).

In the multivariate analysis, only sex, bilirubin and albumin proved to have significant, independent prognostic value (data not shown). When including these variables in the analysis, the sclerotherapy group and the combined therapy groups both showed almost the same, highly significant excess mortality rate, whereas no effect of propranolol was seen (Model C1 and C2, Table 2).

No conspicuous pattern was seen in the causes of death that could be associated with the different mortality rate in the four treatment groups (Table 4). Hepatic failure played a major role as a cause of death (67%) in all four groups.

TABLE 4. Causes of death in patients without transfusion-requiring variceal bleeding

Cause of death[a]	Treatment group: Control n = 8[b]	Sclerotherapy n = 13	Propranolol n = 5	Combined n = 20
Hepatic failure	5	9	4	13
Hemorrhage	1	3	1	4
Pneumonia	1	1	1	3
Other infections	0	1	0	1
Malignancies	2	1	0	3
Kidney failure	0	0	0	3
Biopsy/surgery	0	2	2	3
Pulmonary infarct	0	0	0	1
Unknown	1	2	1	2

[a]Each death may have more than one of these causes.

[b]N = number of deaths.

Total Mortality Rate

The total number of deaths was 74 (26%). Sixteen (22%) were in the control group, 18 (25%) were in the sclerotherapy group, 10 (15%) were in the propranolol group and 30 (41%) were in the combined therapy group. Analysis of the total mortality rate—disregarding the bleeding episodes—showed that the sclerotherapy group and the propranolol group did not differ significantly from the control group, whereas the combined therapy group had a significantly higher mortality rate (Cox regression model, p = 0.03).

Upper Gastrointestinal Bleeding from Non-variceal Sources

Forty episodes were recorded in 25 patients (9%), and 30 episodes in 21 patients (7%) required transfusions (Table 5). More episodes were ascribed to gastritis or gastric erosions in the sclerotherapy groups than in the nonsclerotherapy groups. Otherwise, the pattern of sources of hemorrhages did not reveal any conspicuous pattern across treatment groups. It is noteworthy that no major excess of nonvariceal esophageal bleeding were seen in the sclerotherapy groups.

Complications and Side Effects

The reported complications to sclerotherapy were: esophageal stricture (ten patients); esophageal ulcerations involving more than half the circumference (nine patients); dysphagia (nine patients); mediastinitis with septicemia (one patient); suspected esophageal perforation without clinical consequences (one patient); aphonia (one patient); and recurrent pulmonary embolism (one patient) (37).

The following complications or side effects were ascribed to propranolol treatment: dizziness (nine patients); cold extremities (eight patients); hypotension (seven patients); bradycardia (four patients); orthostatic hypotension (three patients); heart incompensation

TABLE 5. Upper gastrointestinal hemorrhages from other sources than esophageal varices by treatment group

Source of bleeding	Treatment group			
	Control n = 5 (4)[a]	Sclerotherapy n = 5 (4)[a]	Propranolol n = 8 (6)[a]	Combined n = 7 (7)[a]
Esophagitis	1	0	1	1
Esophageal ulcer	0	2	0	0
Mallory-Weiss lesion	1	0	1	0
Gastritis, erosions	0	6	3	4
Gastric ulcer	2	3	2	2
Duodenal ulcer	1	0	2	1
Duodenitis	0	0	2	0
Small intestine[b]	0	2	0	0
Unknown	1	1	0	1
Total	6	14	11	9
Transfusion-requiring	4	12	7	7

[a]Number of patients in whom the episodes occurred; the number of patients requiring blood transfusion are given in parentheses.

[b]The two episodes occurred in one patient, who also suffered from severe coagulopathy.

(three patients); severe tiredness (three patients); worsening of chronic obstructive lung disease (three patients); nightmares (two patients); acute cardiac failure and pulmonary infarction (one patient); abdominal discomfort (one patient); generalized erythema (one patient; it was possibly caused by another drug); and dermatitis (one patient).

DISCUSSION

In this trial, sclerotherapy, propranolol and the combination of the two treatments did not result in any change in the incidence of variceal hemorrhage. The patients in the sclerotherapy groups suffered from a considerable, highly significant excess mortality rate unrelated to variceal hemorrhage, whereas the patients in the propranolol group showed no change in the mortality rate. The course after variceal hemorrhage and the subsequent mortality rate were not significantly improved by the prophylatic treatments. The group receiving the combination of the two treatments exhibited a significant excess total mortality rate.

Prophylaxis against variceal hemorrhage is justified only in patient populations with a recognizable risk of this event, but the acceptable minimum level of risk must depend on the cost, broadly speaking, of the prophylaxis (38). Risk of variceal hemorrhage is related to the size of the varices (39), and several of the previous prophylactic trials have included only patients with "large" varices (11, 15-16, 18, 20-27, 29). We did not restrict our trial to such patients and required only the presence of varices. Patients with "small" varices do run a clinically relevant risk of variceal hemorrhage. In a recent large Italian study the rate was estimated to be between 6% and 44% per year compared with a rate between 15% and 76% for "large" varices, depending on Child class and degree of red-wale markings on the varices (39). The mortality rate after variceal hemorrhage does not depend on the size of the varices (40). Only by the inclusion of patients with "small" varices is it possible to assess whether they might also benefit from prophylaxis. In addition, a considerable observer variation exists in endoscopic assessment of varices (30), and the varices probably vary in size over time also. The overall 1-yr risk of variceal hemorrhage in our study was about 15%, which is the same level of risk as in several other trials of primary prophylaxis, including some selecting patients with "large" varices (13, 17, 20, 22, 26, 27, 29).

In our trial, administration of the treatments and assessment of treatment effects were not blinded for either patients or physicians. As recently emphasized by Conn et al. (28), the double-blind trial design allows assessment of treatment effects separate from placebo effects, and it minimizes bias in the assessment, particularly that implying subjective components for the patient, the observer or both (e.g., symptoms considered complications to the treatment). However, placebo tablets and sham endoscopy procedures would not be realistic alternatives to the tested treatments in clinical practice. Considering the direct effects of both treatments tested (mucosal changes of the esophagus induced by sclerotherapy and systemic hemodynamic effects of propranolol), it would be difficult to maintain blindness. The results of this trial do not raise any suspicion about biases favoring the tested treatments. On the other hand, it seems unlikely that biases could have counterbalanced significant prophylactic effects. The trial started in the background of a recently concluded large trial demonstrating the beneficial long-term effects of sclerotherapy in secondary prophylaxis (41) and the very optimistic early results of primary prophylaxis with both sclerotherapy and propranolol (11, 12, 25).

A recent metanalysis of 13 trials of prophylactic sclerotherapy (11-23), comprising 29 to 282 patients each, suggests that a positive effect is achieved only in patients who have a high inherent risk of variceal bleeding, whereas no effect or even a negative effect is seen when the risk is low (3). Such a beneficial effect is compatible with the unambiguous finding of reduced incidence of recurrent bleedings after sclerotherapy in patients at high risk as indicated by their previous bleeding (3). However, for various methodological reasons, the association between risk of bleeding and prophylactic effect may be questioned (3, 38, 39). The confidence intervals of the effect of sclerotherapy in our trial extended from 0.61 to 1.84 (relative risk ratios), which delineate the possible true treatment effects compatible with our results. Combining our data with those obtained in other trials with similar risk of bleeding in the control group, a value around 1 (i.e., no treatment effect) seems to be the most likely one.

The risk of dying without variceal hemorrhage was significantly increased in the sclerotherapy groups, and, when balance was increased by taking into account

important prognostic covariables, the risk was equally increased in the sclerotherapy and the combined therapy groups. The analysis of the causes of death gave no obvious explanation of the increased mortality rate. In particular, no excess of fatal bleedings were seen from sources other than varices. The proportion of death associated with liver failure was the same in the four treatment groups. A significant excess mortality rate in patients receiving sclerotherapy was also found in the hitherto largest trial in which 282 males admitted to Veterans Affairs hospitals in the United States with alcoholic liver disease were included (17). Koch et al. (13) found that, among patients in Child's classes B and C, those receiving sclerotherapy had a considerable excess mortality rate. We speculate that the repeated sclerotherapy sessions are poorly tolerated by these patients and contribute to the precipitation of liver failure and other common complications of cirrhosis.

The metanalysis of the five clinical trials of β-blockers (three on propranolol and two on nadolol) (25-29), including 79 to 230 patients, strongly supported a prophylactic effect on the risk of bleeding (3, 4, 29). A recently updated metanalysis, including the preliminary results of our study, gave a pooled relative risk of 0.5 with 95% confidence limits of 0.4 to 0.7 (42). A metanalysis based on the individual data from four of the trials (25-27, 29) gave the same result (43). On the other hand, preliminary data from an Australian trial (44) showed a significantly increased bleeding rate in the propranolol-treated group, but the sample size was too small to affect the overall result. Accepting that the effect of propranolol may be assessed in the entire series of our study, the confidence intervals for the effect ranged from 0.53 to 1.60. The confidence interval for the effect of the propranolol group alone vs. the control group ranged from 0.4 to 2.1, which is compatible with the results of the metanalysis.

Except for random sampling variation, no obvious reasons exist for the difference between our result and the previous ones. A high proportion of the patients in our study were alcoholics, which may raise the suspicion of noncompliance with the medication. However, their adherence to the treatment and follow-up program was reasonably good, comparable in the four groups and at about the same level as in the previous trials. Moreover, in the study reported by Conn et al. (28), which enrolled a similar proportion of alcoholics, a highly significant prophylactic effect was found, and according to a detailed account (including clinic attendance, tablet consumption, abstinence from alcohol and propranolol plasma levels) the compliance was fairly good. The heterogeneity of the results may suggest that a subgroup of patients, which the various trials have had different success in targeting, may benefit from treatment with β-receptor blockade. Further studies and analysis of previous studies are needed to identify the characteristics of this group.

The risk of dying without variceal bleeding was not affected by β-receptor blockade in our trial. The metanalysis of the overall mortality rate in the previous prophylactic β-receptor blockade trials showed only a modest and insignificant reduction despite the significant reduction in bleeding risk (3, 4, 42, 43). One of these trials (29) found a borderline significant excess mortality rate. These findings may suggest that the treatment causes some deleterious effects—before or after variceal bleeding—that to some extent counterbalance the benefit of reduced incidence of variceal bleeding. However, our data on the mortality rate without variceal bleeding and case fatality after such bleeding do not support this interpretation. The metanalysis based on individual data (43) found a significant reduction in risk of fatal bleeding. Because variceal bleeding is responsible for only a part of the mortality rate in this patient group, it will, for purely statistical reasons, be much more difficult to demonstrate a reduction in the mortality rate than in bleeding.

In the trials of secondary prophylaxis, no convincing evidence was seen favoring either sclerotherapy or propranolol (3) and, taken together, no support of a benefit by combining the two treatments (5-10). Although we found no treatment effects, this is in agreement with our results. However, a French trial (45) showed a significantly better prophylactic effect of propranolol than of sclerotherapy on bleeding but no significant effects on the mortality rate. This is in accordance with the results of the metanalysis of the effects of either treatment.

It is conceivable that the prophylactic treatment may affect the course and the outcome of the first variceal hemorrhage, but we found no significant effects. In two previous prophylactic trials, one on propranolol (29) and one on sclerotherapy (18), neither found any effect of the prebleeding treatment.

We conclude that sclerotherapy is not suitable for prophylaxis of variceal hemorrhage, either alone or in combination with propranolol. In contrast to other trials, we found no effect of propranolol on the risk of variceal hemorrhage, suggesting that the previously obtained positive pooled estimate of the effect may be somewhat exaggerated.

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