

Propranolol, Isosorbide Mononitrate and Endoscopic Band Ligation – Alone or in Varying Combinations for the Prevention of Esophageal Variceal Rebleeding

Irfan Ahmad¹, Anwaar A. Khan², Altaf Alam², Arshad Kamal Butt², Farzana Shafqat² and Shahid Sarwar³

ABSTRACT

Objective: To compare the efficacy of propranolol, propranolol with nitrate, band ligation, and band ligation with propranolol and nitrate for the prevention of esophageal variceal rebleeding.

Study Design: A prospective randomized trial.

Place and Duration of Study: Department of Gastroenterology and Hepatology, Sheikh Zayed Hospital, Lahore, from November 2003 to July 2005.

Methodology: One hundred and sixty cirrhotic patients with esophageal variceal bleeding were randomized to four treatment groups (propranolol, propranolol plus isosorbide mononitrate, band ligation, band ligation plus propranolol and nitrate) with 40 patients in each group. Patients were followed for 6 months after the enrolment of last patient. Primary end points were recurrence of esophageal variceal bleeding and death. Treatment complications were noted.

Results: Four treatment groups were comparable regarding baseline characteristics. Esophageal variceal rebleeding occurred in 22% patients in band ligation plus drugs group, 26% patients in drug combination group, 31% patients in banding group and 38% patients in propranolol group ($p=0.41$). Difference in mortality rates was also not significant.

Conclusion: There was no significant difference between treatment groups in prevention of esophageal variceal rebleeding.

Key words: Propranolol. Isosorbide mononitrate. Band ligation. Esophageal variceal rebleeding.

INTRODUCTION

Esophageal variceal bleeding is a common cause of upper gastrointestinal bleeding.¹ After an episode of variceal bleeding, there is about 70% risk of rebleeding and mortality rate among these cases is 20-35%.² Therefore, therapeutic measures to prevent rebleeding are essential.^{3,4}

Sclerotherapy has proven beneficial in secondary prevention of variceal bleeding but it has higher rebleeding rate and significant complication rate.^{5,6} Endoscopic band ligation has lower rebleeding and complication rates, and it requires fewer sessions to obliterate varices, so it is the preferred endoscopic treatment for secondary prevention.⁷⁻⁹ Non-selective beta-blockers are well-documented to be effective for

secondary prevention. They are equally or slightly less effective than sclerotherapy.^{6,10} Beta-blockers are also used in combination with oral nitrates and this combination is more effective than beta-blockers alone or sclerotherapy.^{11,12}

Studies that compared combined pharmacological therapy with endoscopic band ligation showed conflicting results;¹³ one showed a benefit of combination pharmacological therapy,⁶ another favoured banding as the most effective secondary preventive measure,¹⁴ and yet another revealed no difference between treatment groups.¹⁵ The aim of this prospective randomized trial was to compare propranolol alone, propranolol combined with oral nitrate, band ligation alone and band ligation combined with propranolol plus oral nitrate for the prevention of esophageal variceal rebleeding.

METHODOLOGY

The study was conducted at the Department of Gastroenterology and Hepatology, Sheikh Zayed Hospital, Lahore, from November 2003 to July 2005.

Cirrhotic patients aged 20-75 years who were admitted with endoscopically proven esophageal variceal bleeding were considered for enrollment in the study. Patients were excluded from the study in case of

¹ Medical Unit 1, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan.

² Department of Gastroenterology and Hepatology, Sheikh Zayed Hospital, Lahore.

³ Department of Gastroenterology, Fatima Memorial Hospital, Lahore.

Correspondence: Dr. Irfan Ahmad, C-4/2, Medical Colony, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan.
E-mail: uhirfan@yahoo.com

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previous endoscopic or drug therapy; any contra-indication to either treatment; bleeding gastric varices or gastropathy; advanced hepatocellular carcinoma, acute on chronic liver disease or any other debilitating disease.

Patients were resuscitated at presentation and band ligation or sclerotherapy was done within 12 hours of admission. Patients were assessed on 5th day of admission and, those who were found eligible for enrollment, were randomly assigned to one of the four treatment groups, using opaque, sealed envelopes, that contained a treatment assignment derived from computer-generated random numbers. In propranolol group, propranolol was started at a dose of 10 mg, thrice daily, which was increased over one week to decrease resting heart rate by 25% but not <55 beats/minutes. In propranolol plus isosorbide mononitrate group, propranolol was given as above and, after achievement of target heart rate, isosorbide mononitrate (ISMN) was added at 10 mg, twice daily, increasing over one week to 20 mg, twice daily, unless side effects (headache, systolic BP<90 mmHg) developed, in which case maximal tolerated dose was given. In the band ligation (EVL) alone group, banding was done using Saeed Six-Shooter at randomization, then every 3 weeks until varices eradicated. Follow-up endoscopy was done every 3 months and a course of banding repeated, if needed. In the band ligation plus propranolol and isosorbide mononitrate group, both banding and drug therapy were instituted as described above.

Patients were followed for 6 months after enrollment of the last patient. Main outcome variables were clinically significant, endoscopically proven recurrent esophageal variceal bleeding (treatment failure) and death. Clinical significant bleeding meant an episode of bleeding which necessitated 2-unit transfusion or if there was a drop in hemoglobin by 2 g/dL. Treatment complications were also recorded.

Study protocol was approved by institutional ethical review committee. A written informed consent was obtained from the patient or relative before enrollment in the study.

Analyses were performed by using SPSS 10 software package (SPSS, Chicago). Quantitative variables were compared by using ANOVA and qualitative variables by using χ^2 test. A p-value of <0.05 was considered significant.

RESULTS

Out of 160 patients, randomized to 4 treatment groups, 10 were excluded from analysis. Seven patients were intolerant to ISMN due to hypotension, one patient developed complete heart block when given propranolol

and 2 were lost in follow-up. The groups were comparable regarding age, gender, cause of cirrhosis, Child-Pugh score/class and size of varices (Table I).

Median duration of follow-up was 260 days in propranolol group (ranging from 29 to 615 days), 287 days in propranolol plus ISMN group (ranging from 45 to 619 days), 256 days in EVL group (ranging from 32 to 614 days) and 292 days in EVL plus drugs group (ranging from 49 to 609 days).

Mean dose of propranolol was 52 ± 22 mg/day (ranging from 20 to 80 mg) in propranolol group, 50 ± 21 mg/day (ranging from 20 to 80 mg) in the propranolol plus ISMN group and 53 ± 21 mg/day (ranging from 30 to 80 mg) in EVL plus drugs group. Mean dose of ISMN was 33 ± 10 mg/day (range=20 mg) in propranolol plus ISMN group and 35 ± 9 mg/day (range=20 mg) in EVL plus drugs group. Patients in EVL group achieved variceal obliteration after a mean of 3.5 ± 1.4 sessions (range=6) of ligation and those in EVL plus drugs group achieved obliteration after 3.0 ± 1.3 sessions (range=5). The duration from start of treatment to obliteration was 62 ± 29 days (ranging from 15 to 164 days) in EVL group and 54 ± 27 days (ranging from 14 to 132 days) in EVL plus drugs group. Variceal recurrence requiring repeat sessions of ligation occurred in 10 patients in EVL group and in 12 patients in EVL plus drugs group.

The rate of significant esophageal variceal rebleeding was highest in propranolol group and lowest in EVL plus drugs group (Table II) but the difference was not significant ($p = 0.41$). Like treatment failure, there was no significant difference between 4 treatment groups regarding mortality rate. Death was related to liver failure in 14 patients (4 each in propranolol and propranolol plus ISMN groups and 3 each in EVL and EVL plus drugs groups) and to recurrent variceal bleeding in 9 patients (4 in propranolol group, 2 each in EVL and EVL plus drugs groups and one in propranolol plus ISMN group). Three patients (one each in propranolol, propranolol plus ISMN and EVL groups) died of hepatorenal syndrome, 2 (one each in EVL and EVL plus drugs groups) died of hepatocellular carcinoma, and 2 (one each in EVL and EVL plus drugs groups) died of sepsis.

Fifteen patients experienced asthenia (7 in propranolol group, 4 each in propranolol plus ISMN and EVL plus drugs groups). Bradycardia (pulse rate <55/minutes) requiring dose reduction to 20 mg/day occurred in 5 patients taking propranolol (4 in propranolol group and one in propranolol plus ISMN group). Eleven patients developed headache (6 in propranolol plus ISMN group and 5 in EVL plus drugs group). Three patients in EVL group and 2 in EVL plus drugs group developed banding site ulcer bleeding. Other complications related to banding were fever (3 patients), retrosternal pain (3 patients) and transient dysphagia (2 patients).

Table I: Baseline characteristics of patients in four treatment groups who were included in the analysis..

Characteristics	P* group (n=39)	P+ISMN**group (n=35)	EVL***group (n=39)	EVL+P+ISMN group (n=37)	p-value
Mean age (years) \pm SD	52.59 \pm 9.54	51.94 \pm 9.10	52.59 \pm 10.40	50.46 \pm 11.33	0.736
Sex					
Male	25	21	25	30	0.356
Female	14	14	14	7	
Causes of cirrhosis					0.743
Hepatitis C	33	31	33	35	
Hepatitis B	4	2	3	2	
Hepatitis B+C	2	2	2	0	
Alcoholism	0	0	1	0	
Active bleeding	19 (48.7%)	12 (34.3%)	14 (35.9%)	17 (45.9%)	0.393
Hemoglobin (g/dL)	9.75 \pm 1.52	9.55 \pm 1.47	9.94 \pm 1.43	9.94 \pm 1.23	0.776
Creatinine (mg/dL)	1.20 \pm 0.45	1.30 \pm 0.63	1.09 \pm 0.32	1.10 \pm 0.27	0.159
Bilirubin (mg/dL)	1.61 \pm 1.03	1.74 \pm 1.10	1.47 \pm 0.96	1.73 \pm 1.26	0.619
PT (seconds)	16.10 \pm 2.73	17.45 \pm 3.30	16.35 \pm 3.67	17.16 \pm 5.77	0.607
Albumin (g/dL)	3.15 \pm 0.55	2.98 \pm 0.40	3.25 \pm 0.58	3.20 \pm 0.31	0.101
Ascites	29 (74.3%)	30 (85.7%)	29 (74.3%)	32 (86.5%)	0.465
Encephalopathy	9 (23.1%)	4 (11.4%)	10 (25.6%)	7 (18.9%)	0.501
Child-Pugh score	8.51 \pm 2.16	9.11 \pm 2.11	8.28 \pm 2.12	8.32 \pm 1.94	0.349
Child-Pugh class					
A	6	2	7	4	0.319
B	23	19	23	27	
C	10	14	9	6	
Vericeal grade****					
1 and 2	15	12	15	15	0.991
3	24	23	24	22	0.990

*Propranolol **Isosorbide mononitrate ***Endoscopic variceal ligation ****Grade 1 denotes varices that flattened with inflation, grade 2 that were not flattened by inflation but occupied less than 1/3 of lumen, and grade 3 that occupied more than 1/3 of lumen.

Table II: Comparison of treatment failure and mortality among four treatment groups.

Variables	P group	P+ISMN group	EVL group	EVL+P+ISMN group	p-value
Treatment failure	15 (38%)	9 (26%)	12 (31%)	8 (22%)	0.41
Mortality	9 (23%)	6 (17%)	8 (20%)	7 (19%)	0.93

DISCUSSION

The results of this study showed that there was no significant difference between the 4 treatment groups in the prevention of esophageal variceal rebleeding, though the rebleeding rate was lowest in the banding plus drugs group and highest in propranolol group. All the treatment groups were similar in baseline characteristics, especially the severity of liver disease and size of varices, which are considered as important predictors of variceal rebleeding, so it is unlikely that insignificant difference between the groups could be ascribed simply to selection bias.

Our results were consistent with previous studies that showed higher rebleeding rate in propranolol group (41%) than in propranolol plus nitrate group (33%) and in band ligation group (35%) than in drug combination group (22%).^{11,15} The differences were not statistically significant in both studies. The higher rebleeding rates in the first study,¹¹ compared with the present results might be due to longer follow-up duration (630 days) but the difference is not great probably because rebleeding generally occurs early. The rebleeding rates in the second study,¹⁵ were similar to those of this study despite the fact that more than half of the patients did

not receive nitrate due to development of side effects. Out of 8 patients excluded from the final analysis, 7 were unable to tolerate nitrates. It means that it is not always possible to add nitrates to β -blockers. Recent trials showed significantly higher rebleeding rate with banding than with banding plus nadolol ($p=0.006$) or banding plus nadolol and sucralfate.^{16,17}

Comparatively lower dose of propranolol were used in this study but the targeted heart rate was achieved in all patients. Four patients developed bradycardia with the starting dose of 30 mg/day and the dose had to be reduced to 20 mg/day. The mean dose of ISMN in this study was similar to that used in other studies.^{11,14} The dose had to be maintained at 20 mg/day in 21 patients as increasing dose resulted in development of hypotension.

Patients receiving repeated band ligation may have higher frequency of fundal varices and worsening of portal hypertensive gastropathy due to increased portal pressure.^{14,18} In contrast, the use of propranolol may provide protection against such complications. Surprisingly, there was no difference in band ligation groups and pharmacological therapy groups in this study regarding such complications. The performance of

the banding procedure by less experienced persons might have an effect on the efficacy of banding.

The mortality rate was not different among the treatment groups and there was no death ascribed to treatment related complications. The present results are similar to the findings of previous studies,^{11,15} although Patch *et al.* reported a higher mortality rate, probably due to longer follow-up duration.¹⁵ The frequency and severity of complications were similar between the 4 treatment groups. Fortunately, most of the complications were mild as in previous studies.

CONCLUSION

Esophageal variceal rebleeding occurred less frequently if propranolol and nitrate were added to band ligation but the difference was not significant when compared with drug combination without banding or banding and propranolol alone. The preventive therapy should be individualized based on cost effectiveness and local expertise in endoscopic therapy and patient preference.

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