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...
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 χ² 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
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
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).
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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>P group (n=39)</th>
<th>P+ISMN group (n=35)</th>
<th>EVL group (n=39)</th>
<th>EVL+P+ISMN group (n=37)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Mean age (years) ± SD</td>
<td>52.59 ± 9.54</td>
<td>51.94 ± 9.10</td>
<td>52.59 ± 10.40</td>
<td>50.46 ± 11.33</td>
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<td>Hepatitis B</td>
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<td>3</td>
<td>2</td>
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<td>Hepatitis B+C</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>Alcoholism</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Active bleeding</td>
<td>19 (48.7%)</td>
<td>12 (34.3%)</td>
<td>14 (35.9%)</td>
<td>17 (45.9%)</td>
<td>0.393</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.75 ± 1.52</td>
<td>9.55 ± 1.47</td>
<td>9.94 ± 1.43</td>
<td>9.94 ± 1.32</td>
<td>0.776</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>1.20 ± 0.45</td>
<td>1.30 ± 0.63</td>
<td>1.09 ± 0.32</td>
<td>1.10 ± 0.27</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.61 ± 1.03</td>
<td>1.74 ± 1.10</td>
<td>1.47 ± 0.96</td>
<td>1.73 ± 1.26</td>
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<td>PT (seconds)</td>
<td>16.10 ± 2.73</td>
<td>17.45 ± 3.30</td>
<td>16.35 ± 3.67</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>3.15 ± 0.55</td>
<td>2.98 ± 0.40</td>
<td>3.25 ± 0.58</td>
<td>3.20 ± 0.31</td>
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<td>Encephalopathy</td>
<td>9 (23.1%)</td>
<td>4 (11.4%)</td>
<td>10 (25.6%)</td>
<td>7 (18.9%)</td>
<td>0.501</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>8.51 ± 2.16</td>
<td>9.11 ± 2.11</td>
<td>8.28 ± 2.12</td>
<td>8.32 ± 1.94</td>
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<td>Child-Pugh class</td>
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<tr>
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<td>6</td>
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<td>Vericeal grade****</td>
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<td>15</td>
<td>15</td>
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<td>24</td>
<td>23</td>
<td>24</td>
<td>22</td>
<td>0.990</td>
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</table>

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>P group</th>
<th>P+ISMN group</th>
<th>EVL group</th>
<th>EVL+P+ISMN group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>15 (38%)</td>
<td>9 (26%)</td>
<td>12 (31%)</td>
<td>8 (22%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Mortality</td>
<td>9 (23%)</td>
<td>6 (17%)</td>
<td>8 (20%)</td>
<td>7 (19%)</td>
<td>0.93</td>
</tr>
</tbody>
</table>
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, although Patch et al. reported a higher mortality rate, probably due to longer follow-up duration. 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.

REFERENCES