The effects of endoscopic variceal ligation and propranolol on portal hypertensive gastropathy: a prospective, controlled trial

Gin-Ho Lo, Kwok-Hung Lai, Jeng-Shiung Cheng, Ping-I Hsu, Tai-An Chen, E-Ming Wang, Chiun-Ku Lin, Hung-Ting Chiang
Taipei, Taiwan

Background: Endoscopic treatment of esophageal varices may accentuate portal hypertensive gastropathy. The impact of the combination of band ligation and propranolol on this condition remains unknown.

Methods: Patients with history of variceal bleeding were randomized to receive band ligation alone (control group, 40 patients) or a combination of band ligation and propranolol (propranolol group, 37 patients). Serial endoscopic evaluation of gastropathy was performed. Gastropathy was classified into 3 grades and scored as 0, 1, or 2.

Results: Before endoscopic treatment, 17% of the control group and 22% of the propranolol group had gastropathy ($p = 0.78$). The occurrence of gastropathy after endoscopic treatment was significantly higher in the control group than in the propranolol group ($p = 0.002$). Serial endoscopic follow-up revealed that the mean gastropathy score was significantly higher in the control group than in the propranolol group ($p < 0.05$). In patients with gastropathy the gastropathy score reached a peak at 6 months after endoscopic treatment in both the control and propranolol groups (85% vs. 48%, respectively). After variceal obliteration, accentuation of gastropathy was significant in the control group ($p < 0.01$) but not in the propranolol group. Gastropathy was less likely to develop in patients who developed gastric varices. Esophageal variceal recurrence was not related to the development of gastropathy after variceal obliteration with banding. Only one patient in the control group bled from gastropathy.

Conclusion: Band ligation of esophageal varices may accentuate gastropathy, which in this study was partly relieved by propranolol. (Gastrointest Endosc 2001;53:579-84.)

In recent years, gastric mucosal lesions have been recognized as an important complication of portal hypertension. A variety of terms including erosive gastritis, acute gastric erosions, and vascular ectasia have been coined to describe these lesions. Because the pathologic change is characterized by vascular ectasia rather than mucosal inflammation, the term congestive gastropathy was coined by McCormack et al. Currently, portal hypertensive gastropathy (PHG) is the preferred term. The prevalence of PHG varies widely; frequencies from 4% to 98% have been recorded in studies of patients with portal hypertension. Endoscopic injection sclerotherapy (EIS) has been identified as one of the factors that may influence the development of PHG. Endoscopic variceal ligation (EVL) is evolving as a preferred technique in the management of bleeding esophageal varices. EVL also has been shown to have a harmful effect on PHG. On the other hand, propranolol was found to be useful in preventing bleeding from congestive gastropathy. This prospective study was conducted to investigate whether the addition of propranolol reduced the development or worsening of PHG after EVL.

MATERIALS AND METHODS

From July 1994 through January 1996, patients admitted with esophageal variceal bleeding were considered for inclusion in the trial. The inclusion criteria were as follows: (1) history of esophageal variceal bleeding; (2) portal hypertension caused by cirrhosis; and (3) age between 20 years and 70 years. Patients were excluded from the study if any of the following conditions were present: (1) active variceal bleeding during emergency endoscopy; (2) hepatocellular carcinoma, other malignancy, uremia, or other debilitating disease that might reduce life expectancy; (3) gastric varices or severe PHG on initial endoscopy; (4) refractory ascites, hepatic encephalopathy, or marked
jaundice (serum bilirubin >10 mg/dL); (5) prior EIS or therapy with beta-blockers; (6) history of shunt operation or transjugular intrahepatic porto-systemic stent shunt; or (7) inability to undergo regular endoscopic follow-up.

All eligible patients underwent EVL until variceal obliteration was achieved. Patients were randomized to receive propranolol or serve as control subjects. Randomization was based on a system of random numbers. Opaque serially numbered envelopes were used. Randomization was performed soon after the initial EVL. Informed consent was obtained from all patients.

The severity of liver disease for each patient was assessed at presentation according to Pugh’s modification of Child’s classification.16 The assessment of variceal size was based on the classification of Beppu et al.17

EVL and administration of propranolol

EVL was performed by using the endoscopic ligating device (Bard Interventional Products, Billerica, Mass.) and a standard endoscope (XQ-20, Olympus Optical Co., Tokyo, Japan) as described elsewhere.11 Briefly, ligation was performed at 1 to 5 cm proximal to the gastroesophageal junction. Each varix was ligated with 1 to 3 bands. Individual ligation sites were gradually reduced. Patients underwent a second session of treatment at 7 to 10 days after the initial treatment. They were then discharged and followed as outpatients. Further treatment sessions were performed at 3-week intervals until all varices were obliterated.

Table 1. Characteristics of study groups

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Propranolol group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>40</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55 ± 13 (35-70)</td>
<td>57 ± 14 (38-70)</td>
<td>0.77</td>
</tr>
<tr>
<td>Men/women</td>
<td>35/5</td>
<td>31/6</td>
<td>0.75</td>
</tr>
<tr>
<td>Etiology of cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>11 (27%)</td>
<td>12 (32%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Posthepatitis</td>
<td>26 (65%)</td>
<td>21 (57%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Primary biliary</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>1</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>2.8 ± 0.4</td>
<td>2.7 ± 0.5</td>
<td>0.83</td>
</tr>
<tr>
<td>Bilirubin (gm/dL)</td>
<td>2.6 ± 0.7</td>
<td>2.8 ± 0.8</td>
<td>0.76</td>
</tr>
<tr>
<td>Child-Pugh class (A/B/C)</td>
<td>4/21/15</td>
<td>3/18/16</td>
<td>0.87</td>
</tr>
<tr>
<td>Variceal size (F2/F3)</td>
<td>11/29</td>
<td>18/19</td>
<td>0.06</td>
</tr>
<tr>
<td>Gastropathy</td>
<td>7 (17%)</td>
<td>8 (22%)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Table 2. Results of treatment

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Propranolol group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVL sessions</td>
<td>3.6 ± 1.1 (2-5)</td>
<td>3.3 ± 0.8 (2-5)</td>
<td>0.35</td>
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<tr>
<td>Obliteration of varices</td>
<td>80%</td>
<td>84%</td>
<td>0.77</td>
</tr>
<tr>
<td>Bands consumed</td>
<td>16 (7-20)</td>
<td>15 (8-21)</td>
<td>0.70</td>
</tr>
<tr>
<td>Recurrent bleeding from EGV</td>
<td>12 (30%)</td>
<td>9 (24%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Recurrent bleeding from PHG</td>
<td>1 (2%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PHG score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before EVL</td>
<td>0.2 ± 0.1 (0-2)</td>
<td>0.2 ± 0.1 (0-2)</td>
<td>1</td>
</tr>
<tr>
<td>At variceal obliteration</td>
<td>1.0 ± 0.4 (0-2)</td>
<td>0.5 ± 0.2 (0-2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Development of gastric varices</td>
<td>8 (20%)</td>
<td>5 (13%)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

EGV, Esophagogastric varices; PHG, portal hypertensive gastropathy.

Propranolol

A dose of 10 mg of propranolol was initially given 3 times daily and then adjusted to reduce the baseline resting heart rate by 25% or to a minimum of 55 beats per minute. Compliance was assessed by the reduction in pulse rate and by quantifying the number of tablets consumed. Propranolol was continued until variceal bleeding recurred, death occurred, or the study ended (18 months after enrollment).

Endoscopic examination of the stomach

Before treatment and during follow-up, endoscopic examination of the stomach was performed. The fundus was carefully examined with retroflexion of the endoscope. All lesions including PHG, ulcers, or gastric varices including their distribution were recorded. After variceal obliteration, endoscopy was performed every 3 months. Serial endoscopic findings of PHG were classified according to the criteria of McCormack et al.2: mild (snakeskin pattern, superficial reddening, or fine pink speckling) or severe (cherry-red spots or spontaneous bleeding). A score of 0, 1, and 2 was given to patients with no PHG, mild PHG, and severe PHG, respectively. Endoscopic findings were recorded in each patient and the grades of PHG were assessed by two experienced endoscopists. Endoscopists were blinded as to which group each patient belonged. The PHG score of each patient was decided based on a discussion between the endoscopists. Additionally, there was an assistant who recorded the results. If a
patient had PHG that differed in severity at different sites, the most severe score was recorded. Patients in each group were followed for at least 1 year. The primary objective of the study was the assessment of the prevalence of PHG after EVL. The secondary endpoint was worsening of PHG after EVL.

The data were expressed as mean ± SD. The analysis of data was based on intention-to-treat principle. Mean values of continuous variables were compared with Student’s t test. Discrete variables were analyzed with chi-square test or Fisher’s exact test when appropriate. Kaplan-Meier estimates of PHG developed after the start of the trial were computed. The log-rank test was used to examine the difference between the resultant curves. One-way analysis of variance (ANOVA) was used for intergroup comparisons. P values resulting from multiple comparisons were adjusted with Bonferroni’s correction so that the overall level of significance would remain at the 0.05 level.

RESULTS

The propranolol group comprised 37 patients and the control group 40 patients. Both groups were comparable with regard to baseline characteristics (Table 1). Seventeen percent of the control group and 22% of the propranolol group had mild PHG on enrollment. According to the exclusion criteria, patients who had severe PHG before the start of treatment were excluded. The median follow-up period was 1 year and 5 months. Three patients in the control group and 2 patients in the propranolol group did not comply with the follow-up protocol.

In the propranolol group, the mean dose of propranolol was 96 ± 20 mg per day (range 40-180 mg). The number of sessions required and bands consumed to achieve variceal obliteration was similar between the groups. Also, the rates of variceal obliteration were not significantly different between the groups (Table 2). The duration of time from the start of treatment to obliteration was 46 ± 11 days in the control group and 42 ± 10 days in the propranolol group (p = 0.75).

Twelve patients (30%) in the control group and 9 patients (24%) in the propranolol group had recurrent bleeding from esophagogastric varices (p = 0.62). One patient in the control group with initially mild PHG experienced recurrent bleeding from gastropathy. The bleeding site was localized to the fundus. The episode was controlled by somatostatin infusion for 48 hours.

PHG scores were similar before EVL in both groups; however, PHG scores were significantly higher in the control group at variceal obliteration (Table 2). Sixty-seven percent of the control group and 31% of the propranolol group had PHG at variceal obliteration (p < 0.05). The sites of PHG were predominately in the fundus in both groups (80% control group vs. 89% propranolol group, p = 0.72).

Figure 1 shows the percentage of patients who remained free from gastropathy during serial endoscopic follow-up. The frequency of PHG was significantly greater after endoscopic treatment in the control group compared with the propranolol group (p = 0.002). Gastropathy in patients with this finding reached a peak at 6 months after endoscopic treatment in both the control and propranolol groups (85% vs. 48%, respectively). However, the frequency of PHG was gradually reduced and the difference became insignificant 12 months after randomization. The worsening of PHG also reached a peak at 6 months after enrollment. During that period, 9 patients in the control group and 2 in the propran-

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Figure 1. Percentage of patients without gastropathy during serial endoscopic follow-up. The proportion of patients who developed PHG after endoscopic treatment was significantly higher in the control group than in the propranolol group.

Figure 2. Serial change of mean portal hypertensive gastropathy score in both treatment groups. The black bars represent the control group, and the shaded bars represent the propranolol group. The mean PHG score was significantly higher in the control group as compared with the propranolol group at 3 to 9 months after initiation of endoscopic treatment (p < 0.05, multiple comparisons, star means significant).
olol group had severe PHG. Among them, 6 in the control group and 1 in the propranolol group had mild PHG before the start of EVL. The accentuation of the severity of PHG after variceal obliteration was significant in the control group ($p < 0.01$, ANOVA), whereas no significant difference existed in the propranolol group. Figure 2 shows the mean scores for PHG in both groups. Also, the mean scores were significantly higher in the control group than in the propranolol group after endoscopic treatment ($p < 0.05$, multiple comparisons).

At 12 months follow-up, 13 patients had developed gastric varices, 8 in the control group and 5 in the propranolol group ($p = 0.55$). Three of the 13 patients (23%) had mild PHG, but none had severe PHG. By contrast, 19 of the 29 patients (65%) without gastric varices had PHG, 4 of them severe ($p < 0.01$). Among patients in whom variceal obliteration was achieved, 13 (43%) in the control group and 11 (38%) in the propranolol group had variceal recurrence ($p = 0.73$). Among patients with variceal recurrence, the frequency of PHG was 54% in the control group and 36% in the propranolol group ($p = 0.48$). The frequency of PHG among patients with variceal recurrence (46%) was lower in patients without variceal recurrence (61%) at 1-year follow-up, but this did not reach statistical significance ($p = 0.56$).

The occurrence of PHG appeared to have no relation to Child-Pugh class. In the control group, at 6 months after enrollment, 80% of patients with Child's A cirrhosis, 86% with Child's B, and 85% with Child's C cirrhosis had PHG. In the propranolol group, the proportions of patients with Child's A, B, and C cirrhosis were 40%, 46%, and 57%, respectively ($p = 0.67$). Similarly, the etiology of cirrhosis did not influence the presence of PHG. In the control group, 86% of patients with alcoholic cirrhosis and 90% of those with post-hepatitic cirrhosis had PHG. In the propranolol group, 40% of patients with alcoholic cirrhosis and 50% of those with post-hepatitic cirrhosis had PHG ($p = 0.58$). The number of sessions required for variceal obliteration was $3.7 \pm 1.0$ among patients who had PHG and $3.2 \pm 1.2$ among those who did not ($p = 0.25$).

**DISCUSSION**

Upper GI bleeding is frequently encountered in patients with portal hypertension. Apart from esophagogastroduodenal varices, PHG is an important source of hemorrhage. The pathogenesis of PHG is complex, and enhanced or reduced splanchnic blood flow, humoral factors, local disturbances in the regulation of vascular tone, and high portal pressure have been implicated.

EVL is a well-established method for management of bleeding esophageal varices. In recent years, EVL has become the endoscopic treatment of choice for patients with bleeding esophageal varices. Aggravation of congestive gastropathy after EVL has been reported. Similarly, EVL may also accentuate PHG. The reasons for aggravation in PHG after repeated endoscopic therapy are poorly understood. It may be related to an acute blockage of the gastric mucosal blood flow or enhanced portal pressure. Whether the development of PHG after endoscopic therapy may influence outcome is an issue of concern.

In this controlled trial, our investigation looked at whether propranolol influenced the occurrence of PHG after endoscopic therapy. Our results showed that the development of PHG reaches a peak at 6 months after EVL, the frequency rising from 18% to 85%. In contrast, the prevalence of PHG rose from 22% to 48% in the patients receiving additional therapy with propranolol. The difference was statistically significant. In addition, severe gastropathy was also more frequently encountered in the patients who did not receive propranolol. This implies that EVL may accentuate PHG with respect to frequency as well as severity. With propranolol treatment, the frequency as well as the severity of PHG may be greatly reduced.

The proportion of patients with PHG reached a peak after 6 months of endoscopic treatment of esophageal varices. This is consistent with most reports. It is presumed that gastric capillary ectasia develops with obstruction of the esophageal varices. After a longer period of observation, PHG may improve, possibly because of development of other collaterals. This may explain why the proportion of patients with PHG was gradually reduced and the difference became insignificant 12 months after randomization. On the other hand, it also may be due to smaller sample size during the observation period. As shown in our study, patients who developed gastric varices were less likely to have severe PHG. Patients with esophageal variceal recurrence also had a lower frequency of PHG than patients without variceal recurrence. The difference was not statistically significant, possibly because of the small sample size.

Bleeding from PHG can be slow and insidious or massive and life-threatening. With regard to the treatment of PHG, beta-blockers, portocaval shunt, and the transjugular intrahepatic portosystemic stent shunt have been applied successfully in some patients. Beta-blockers have the advantage of convenience and relatively low cost. Therapy with propranolol has been demonstrated to...
reduce portal pressure and blood flow in the portal venous system.\textsuperscript{31,32} Propranolol was shown to stop bleeding from PHG as well as to prevent recurrent bleeding from severe PHG.\textsuperscript{14,15} Our study confirmed that propranolol may be used to prevent PHG in patients who are predisposed to its development.

Only one patient in the control group bled from PHG. Fortunately, the episode was mild and was arrested by using somatostatin infusion. The low incidence of bleeding from PHG in patients undergoing endoscopic treatment of varices was similar to that of previous reports.\textsuperscript{9,11,12} That is why administration of propranolol did not significantly reduce bleeding from PHG. On the other hand, propranolol has been used to enhance efficacy of EIS in the prevention of variceal recurrent bleeding.\textsuperscript{33,34} Our study showed that patients receiving additional propranolol had a lower frequency of recurrent variceal bleeding; however, the difference was not statistically significant. This also may be related to small sample size. Therefore, in patients undergoing repeated EVL, combining this treatment with propranolol may have the advantage of reducing the frequency of PHG and the frequency of recurrent bleeding, from either PHG or esophageal varices.

In conclusion, EVL may accentuate the development of PHG. With administration of propranolol after esophageal variceal ligation and obliteration, the frequency of portal hypertensive gastropathy may be significantly reduced.

REFERENCES

28. Sarfeh JJ, Juler GL, Stemmer EA, Mason GR. Results of surgical management of hemorrhagic gastritis in patients with

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