Association of Endoscopic Esophageal Variceal Ligation with Duodenal Ulcer

Ze-Hao Zhuang¹, Ai-Fang Lin¹, Du-Peng Tang¹, Jing-Jing Wei¹, Zheng-Ji Liu², Xiao-Mei Xin² and Yu-Feng Pan¹

ABSTRACT

Objective: To determine the frequency of duodenal ulcer (DU), as well as other clinical characteristics occurring after endoscopic variceal ligation (EVL) of the esophagus.

Study Design: Descriptive study.

Place and Duration of Study: The First Affiliated Hospital of Fujian Medical University, Fuzhou, China, from April 2012 to April 2013.

Methodology: A total of 47 patients with esophageal varices (EVr) who had also undergone EVL and gastroscopic follow-up within 3 months of the procedure was retrospectively analyzed. Sixty EVr patients without EVL treatment, but with clinical data available, served as the control group.

Results: The frequency of DU in the EVL group (29.8%, 14/47) was higher than the control group (6.7%, 4/60) (p=0.02). Hp infection rate in EVL group was 19.15% (9/47), while in control group was 21.67% (13/60) (p=0.813). Hp positive rate (12.5%, 1/8) in patients exhibited new DUs after EVL was comparable to the patients without DU in the EVL group (12.1%, 4/33) (p=1.00). Patients with DU after EVL received 18.79 ±8.48 of ligating bands, while in those who did not exhibit DUs received 13.85 ±6.48 (z = -2.042, p = 0.041). Logistic regression analysis showed that the occurrence of DU was not associated with age, gender, Child-Pugh classification, or the grade of PHG (p > 0.05).

Conclusion: Esophageal EVL is associated with a higher frequency of developing DU, which is related to a larger number of applied bands but is not correlated with Hp infection status or other variables.


INTRODUCTION

Portal hypertension, a hemostatic pathology often caused by liver cirrhosis, is known to precipitate several other severe gastrointestinal (GI) complications.¹,² Among the most serious of these complications are gastroesophageal varices (EVr).³,⁴ Bleeding from these varices is associated with high mortality, even in cases where bleeding is controlled through medical intervention.⁵ At present, the preferred treatment modality for attenuating EVr bleeding is endoscopic variceal ligation (EVL).⁶ EVL is effective at controlling active bleeding from such varices with, reputedly, few undesirable side-effects.⁷

There are, however, several possible undesirable complications associated with EVL. These include dysphagia, esophageal strictures, local ulcerations, and transient chest discomfort.⁸,⁹ Conclusions regarding more specific pathological GI outcomes are difficult to draw from the existing studies. For example, research is inconclusive regarding the increased severity of portal hypertensive gastropathy (PHG), and studies focused on portal hypertensive colonopathy are rare. Hence, this study was undertaken in order to investigate a possible association between patients with EVr receiving EVL and a specific GI outcome, namely the increased risk of duodenal ulcer (DU).

METHODOLOGY

Between April 2012 and April 2013, an analysis was conducted of 84 medical histories of patients with esophageal varices who received EVL at the Department of Endoscopy, the First Affiliated Hospital of Fujian Medical University (China). Patients with severe gastric varices received tissue adhesive injection according to the standard treatment protocol; these patients were excluded to rule out a possible mixed effect. Ultimately, 47 of these 84 patients whose clinical data was complete were studied in detail. A flow chart of study participants is shown in Figure 1. Collected clinical data included pretreatment and gastroscopic follow-up within 3 months after EVL. Also recorded were the age and gender of the patients, their infection status with respect to Helicobacter pylori (Hp), number of ligations and ligating bands employed during EVL, Child-Pugh scores, and the grades of PHG (Table I). The
determination of Hp infection status required a rigorous three-test detection protocol. All patients received a rapid urease test, and those tests resulting in a negative outcome, such patients subsequently underwent a 14C urea breath test. If this breath test was also negative for Hp, such patients then underwent tissue biopsy of the gastric antrum for histological examination. Hp infection was excluded only when all three tests were negative, i.e. a positive result for any one of these three tests was interpreted as supporting a diagnosis of Hp infection. Since DU is a common disease, it would appear to be valuable to estimate the current incidence of DU in patients with severe EVr in the same area. Clinical data collected from 60 cases of continuously enrolled patients with severe EVr (with a variceal size larger than 5 mm or occupying more than one-third of the esophageal lumen), but who had not received EVL comprised the control group. Local medical ethics committees approved the study, and all patients provided written informed consent. Clinical conditions indicating EVL intervention included acute EVr hemorrhage(s), previous history of EVr hemorrhage, recurrence of EVr after other surgical treatments, and having one or more conditions that contra-indicated other surgical or radiological shunting therapies. Upper-GI endoscopy and EVL were performed in all patients using an endoscope (GIF-XQ260, Olympus, Tokyo, Japan) loaded with a ligator (SpeedBand SuperView Super 7™ Multiple Band Ligators, Boston Scientific, Natick, MA, or Saeed Six-Shooter, Cook Medical, Winston-Salem, NC). The morphology of the esophagus, stomach, and duodenum, were observed prior to ligation. A small sample of gastric antrum tissue was collected as the substrate for an Hp rapid urease test and subsequent microscopic observation. The ligator was subsequently loaded, and a dense ligation was applied from distal to proximal, starting with the gastroesophageal junction. Endoscopic ligation was re-applied one month later. If necessary, repeat treatments were performed until no further venous varicosities were detectable. Statistical analysis was performed using the 19.0 SPSS software (IBM, Inc.). Data for EVL procedure and the number of employed ligating band were presented as median (25th, 75th percentile). A t-test was used for comparison of differences in measurement data. For categorical variables, either a chi-square test or Fisher’s exact test for four-fold table and a Mann-Whitney test or Wilcoxon signed ranks test for rx2 single ordinal contingency table were employed. A logistic regression model was used to analyze the influence of various factors on the occurrence of DU. Differences with a p-value < 0.05 were considered statistically significant.

RESULTS

A total of 84 patients underwent EVL. Twenty of these individuals (23.81%) received emergent hemostasis, while the other 64 (76.19%) required secondary prophylaxis. All patients had not previously received EVL during their enrollment. To rule out the possible DU missing, caused by emergent hemostasis, patients without satisfactory duodenal observation due to the present of blood were excluded. The patients without follow-up data were likewise excluded. Forty-seven (55.9%) of these 84 patients, whose clinical data was complete, comprised the EVL group. The cohort included 36 (76.60%) males and 11 (23.40%) females, with a mean age of 51.3 ±11.5 years, ranging from 21 to 75 years. Nine (19.15%) of these 47 patients in the EVL group had received emergent hemostasis. Additionally, these 47 patients were divided into three classes according to the Child-Pugh classification system10 for liver dysfunction: Class A (15 cases), B (23 cases), and C (9 cases). Endoscopic diagnosis of PHG was made using a method described by the New Italian Endoscopic Club (NIEC).11 Twenty-seven of these 47 patients had received only one EVL procedure, 15 had received 2, and 5 had received more-than-two. Four of these patients suffered repeat variceal bleeding during a 3-month follow-up and, therefore, underwent an additional EVL procedure during this follow-up period.

There was no difference in the basic characteristics of the patients between the EVL and control groups (p > 0.05, Table I). In addition, within the EVL group, no significant difference was found with respect to PHG grades before and after EVL treatment (p=0.470, Table II).

Most notably, the incidence of DU in the control group was 6.7% (4/60), which did not differ statistically from the incidence in all patients receiving endoscopic examination during the same period (6.9%, 597/8652, p=1.00), within the Department of Endoscopy, The First Affiliated Hospital of Fujian Medical University. In contrast, within the EVL group, 14 patients presented
with DU (29.8%, 14/47), an incidence significantly higher than the control group (6.7%, 4/60, p=0.002). All the ulcers in EVL group were at A2 stage, with diameters ranging from 0.3 cm to 0.6 cm, and 7 of the 14 cases had mild epigastric pain. These 14 included 8 new cases of DU arising after EVL treatment, and 6 cases presenting with DU at the time of band ligation.

With respect to Hp-infection status, no difference was found between the EVL group (19.1%, 9/47) and the control group (21.7%, 13/60, p=0.813). In addition, the Hp infection rate in the 8 new cases of DU, arising after EVL treatment (12.5%, 1/8), was comparable to that in patients without DU in the EVL group (12.1%, 4/33, p=1.00). Hp infection was found in 3 of the other 6 patients with DU observed before EVL.

Also notable is the observation that the number of ligating bands employed in EVL patients with DU was higher than those patients without DU (14 vs. 14, z = -2.042, p=0.041). On the other hand, no significant difference was found in the mean EVL procedures between the EVL group with or without DU (1.5 v/s 2, z = -0.348, p=0.728). Finally, a logistic regression analysis revealed that there was no correlation in the EVL group between the occurrence of DU and patients' age, gender, Child-Pugh classification and PHG grades, respectively (p > 0.05, Table III).

**DISCUSSION**

The preferred treatment for bleeding from esophageal varices, EVL is widely utilized in patients presenting clinically with this condition. In this study, it was found that the percentage of patients receiving EVL for treatment of esophageal varices and who also exhibited DU, was significantly higher than that in a control group of patients who did not receive EVL. Given that there was no difference in the percentage of patients with DU between the control group and all patients undergoing endoscopic examination in the same hospital unit over the same period (6.9%), these results indicate that the mere presence of esophageal varices does not in itself increase the risk of DU occurrence. In contrast, the significantly higher percentage of patients exhibiting DU after EVL treatment strongly suggests that EVL treatment itself increases the incidence of DU.

Although many studies have concluded that Hp infection is a major cause of DU, this study found no significant difference in the ratio of Hp-positive patients between the EVL group and the control group. Furthermore, among those patients who developed DU subsequent to EVL treatment, the percentage of Hp-positive patients was comparable to that of patients who did not develop DU after EVL treatment.

Bleeding and concomittant medicine usage (e.g., somatostatin and its analogues, proton pump inhibitors) can affect the results of both the rapid urease test and the 14C urea breath test during acute stages of hemorrhaging. Hence, a special accommodation was necessary for the 9 patients who underwent emergent hemostasis for such bleeding. For these 9 cases with Hp-negative results through the above two tests, microscopic examination of gastric antrum tissue for Hp was performed, and these results were also negative, confirming an accurate diagnosis for Hp status. All the patients in follow-up examinations received a rapid urease test for Hp during periods when acute hemorrhaging was absent, as well as after withdrawal of proton pump inhibitors for more than one month; no new Hp-positive patient presented. These data support the conclusion that the increased risk of DU is independent of the Hp-infection status of patients in the EVL group.

### Table I: Basic characteristics of the patients in endoscopic variceal ligation (EVL) and control group.

<table>
<thead>
<tr>
<th></th>
<th>Endoscopic variceal ligation (EVL) (n=47)</th>
<th>Control group (n=60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.3 ±11.5</td>
<td>50.7 ±10.6</td>
<td>0.781</td>
</tr>
<tr>
<td>Male**</td>
<td>36 (76.6)</td>
<td>44 (73.3)</td>
<td>0.823</td>
</tr>
<tr>
<td>Child-Pugh classification***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (n, %)</td>
<td>15 (31.9)</td>
<td>23 (38.3)</td>
<td>0.318</td>
</tr>
<tr>
<td>B (n, %)</td>
<td>23 (48.9)</td>
<td>30 (50.0)</td>
<td></td>
</tr>
<tr>
<td>C (n, %)</td>
<td>9 (19.2)</td>
<td>7 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Portal hypertensive gastropathy (PHG) grades***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or mild (n, %)</td>
<td>40 (85.1)</td>
<td>44 (73.3)</td>
<td></td>
</tr>
<tr>
<td>Moderate (n, %)</td>
<td>4 (8.5)</td>
<td>12 (20)</td>
<td>0.171</td>
</tr>
<tr>
<td>Severe (n, %)</td>
<td>3 (6.4)</td>
<td>4 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Pathogenesis**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus-related cirrhosis</td>
<td>42</td>
<td>52</td>
<td>0.771</td>
</tr>
<tr>
<td>Other causes (n)</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

* t-test; ** chi-square test; *** Mann-Whitney test.

### Table II: Comparison of portal hypertensive gastropathy (PHG) grades before and 3 months after endoscopic variceal ligation (EVL) treatment.

<table>
<thead>
<tr>
<th></th>
<th>Portal hypertensive gastropathy (PHG) (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None or mild</td>
</tr>
<tr>
<td>Pre-endoscopic variceal ligation (EVL)</td>
<td>47</td>
</tr>
<tr>
<td>Post-endoscopic variceal ligation (EVL)*</td>
<td>47</td>
</tr>
</tbody>
</table>

*Wilcoxon signed ranks test: compared with pre-endoscopic variceal ligation (EVL). z = -0.722, p = 0.470

### Table III: Results of a logistic regression analysis of the potential factors influencing the occurrence of DU.

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Child-Pugh Classification</th>
<th>PHG grades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>p-value</td>
<td>0.103</td>
<td>0.746</td>
<td>0.158</td>
</tr>
</tbody>
</table>
Proton pump inhibitors were routinely used only in patients with acute EVr hemorrhages for less than 5 days and no patient received NSAIDs before or during the period of study. Therefore, there was no direct evidence showing that the different incidences of DU were associated with gastric acid inhibition during the treatment.

In another group of studies, conducted in the same region as the present research, investigators have found that the prevalence of Hp infection was 51.4% - 59.4% in a population of people receiving gastroscopy, a result much higher than that of EVr patients in this study. Given that the aforementioned research discovered that Hp infection was most common in childhood, acquired by close contact with a carrier, the majority of Hp-infected individuals in that study appeared to be long-term carriers of the bacterium, beginning at an early age.

By comparison, in this study, the leading cause of portal hypertension was a long-term chronic cirrhosis caused by hepatitis B virus infection, and EVr did not occur until adulthood. Therefore, the occurrence of EVr patients with low Hp infection might suggest a change in the environment of the stomach in patients with portal hypertension that created a situation unfavourable for Hp survival. Yet another study on patients with hepatic portal hypertensive gastropathy found the rate of Hp infection to be 23.4% - 31.3%, which is more consistent with our results. In addition, in that study, repeated endoscopic interventions did not increase the infection risk of Hp for patients undergoing EVL. It therefore demonstrated that existing disinfection methods can avoid the spread of Hp during endoscopic examination and treatment, thereby ruling out the possibility as potentially affecting the determination of accurate Hp infection data.

The incidence of DU occurrence in our EVL group was not correlated with age, gender, Child-Pugh classification, and PHG grades (p > 0.05, Table III), but was related to the number of ligating bands introduced during EVL. Since there was a direct correlation between the number of ligating bands and the extent/severity of EVr, one can speculate that there may be a positive correlation between the number of ligating bands and the impact of EVL treatment on the hemodynamics of collateral circulation in patients with portal hypertension.

Congestion and edema of the stomach wall as well as open and direct artery-vein anastomoses within the gastric submucosa with microcirculatory disturbances can lead to damage the gastric mucosal defensive barrier, which is accompanied by PHG when portal hypertension occurs. However, there is no general agreement among researchers with regard to whether or not the collateral circulatory hemodynamic changes in portal hypertension induced by EVL exacerbate the extent of PHG. Yüksel and colleagues suggested that EVL could exacerbate PHG extent, but Yoshikawa et al. took the opposite view. The present results are consistent with the view that EVL will exacerbate PHG. However, in this study, there was no simple and recognizably reliable means to measure portal venous pressure, and it was, therefore, difficult to rigorously compare baseline pressures in these EVL patients. Thus, the effects of EVL on PHG need to be further explored.

In the past, portal hypertension-related intestinal mucosa injury was not taken as seriously as it is now. Recently, some scholars have recommended endoscopic duodenal mucosa erythema (spot or diffuse), mucosal edema (erosion or ulceration) and vascular lesions (varicose veins or telangiectasia) as diagnostic criteria for portal hypertensive colonopathy. Reports on the effect of EVL on duodenal mucosa integrity have been rare. In this study, the incidence of DU increased significantly. This increase was, however, not related to Hp infection but rather to the use of a higher number of ligating bands. The authors surmise that changes to collateral circulation during portal hypertension may be the key mechanism involved. For example, portal hypertension can induce dilatation of the vessels in the duodenal bulb, and EVL may exacerbate the high capacity and low perfusion of the duodenal bulb and injury to the bulb mucosa caused by hypoxia. Moreover, more studies are clearly required to elucidate the impacts of EVL on environmental changes within the stomach, as well as on the secretion of glucagon, gastrin, prostaglandin, vasoactive peptide, histamine, other gastrointestinal hormones, and gastric acid and pepsin. EVL may also impact abnormalities in gastrointestinal peristalsis and the longevity of exposure of the duodenum to injurious substances. In addition, whether sclerotherapy, an alternative procedure, may also provoke a high incidence of DU and should be investigated in patients with EVr.

CONCLUSION

EVL increased the frequency of DU in EVr patients, which was related to the number of ligating bands employed during EVL, but was not related to Hp infection. However, this study was limited by the small numbers and retrospective non-randomly controlled design. Therefore, the exact mechanism by which EVL increases the incidence of DU must be subjected to further investigation.

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REFERENCES


