Pantoprazole Reduces the Size of Postbanding Ulcers After Variceal Band Ligation: A Randomized, Controlled Trial

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Elective esophageal variceal ligation (EVL) is performed to decrease the risk of variceal hemorrhage. Side effects of EVL include hemorrhage, chest pain, dysphagia, and odynophagia. Because gastric acid may exacerbate postbanding ulcers and delay healing, proton pump inhibition may decrease side effects associated with EVL. The aim of this study was to assess the efficacy of pantoprazole, a proton pump inhibitor, as an adjunct to elective EVL. We performed a double-blinded, randomized, placebo-controlled trial of pantoprazole after elective EVL. Subjects in the pantoprazole arm received 40 mg pantoprazole intravenously after EVL followed by 40 mg oral pantoprazole for 9 days. Control subjects received intravenous and oral placebo. Subjects underwent upper endoscopy 10 to 14 days after banding. Primary outcomes included the size and number of ulcers and the subjects' reports of dysphagia, chest pain, and heartburn. Forty-four subjects were randomized: 42 completed the protocol. At follow-up endoscopy, the mean number of ulcers was similar in the two groups. However, the ulcers in the pantoprazole group were on average half as large as in the placebo group (37 mm^2 vs. 82 mm^2, $P < .01$). Chest pain, dysphagia, and heartburn scores were not significantly different. Four subjects, all in the placebo group, had adverse outcomes, including 3 who bled from postbanding ulcers and 1 with sepsis. In conclusion, subjects receiving pantoprazole after elective EVL had significantly smaller postbanding ulcers on follow-up endoscopy than subjects receiving placebo. However, the total ulcer number and patient symptoms were not different between the groups. (HEPATOLOGY 2005;41: 588-594.)

Endoscopic variceal ligation (EVL) was originally developed for the treatment of hemorrhoids.[1-3] It involves the placement of elastic O-ring ligatures over esophageal varices, causing strangulation of the vessels. Proposed for the treatment of esophageal varices as a method for obtaining hemostasis in acute bleeding,[4] EVL has also been used electively for the prophylaxis of recurrent variceal bleeding. It has been proposed as a standard of care to electively perform serial sessions of EVL to obliterate varices in patients with a history of hemorrhage from esophageal varices.[5]

The use of EVL has been favored over endoscopic sclerotherapy because it has a similar efficacy in achieving hemostasis but with fewer complications.[4,6-8] Approximately 3 to 7 days after banding, the strangulated varix sloughs off, leaving a shallow ulcer that typically heals in 14 days.[9] The frequency of deep esophageal injury is low, although transmural necrosis with subsequent mortality has been reported after band ligation.[10,11] Significant bleeding from postligation ulcers occurs in 2% to 5% of patients.[4,7]

Despite the low incidence of local ulcer-related complications inherent in EVL, some authors advocate acid suppression therapy after EVL,[12] reasoning that even physiological acid exposures might retard ulcer healing. However, no data exist evaluating the role of aggressive acid suppression after EVL. Proton pump inhibitors are the most potent pharmacological agents for inhibition of

Abbreviation: EVL, endoscopic variceal ligation.

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gastric acid secretion. Therefore, these agents are the logical candidates to assess the effect that gastric acid plays in post-EVL complications. The aim of the current study was to assess the use of acid suppression with proton pump inhibitors in the setting of elective variceal band ligation.

Patients and Methods

Methods. We performed a randomized, double-blinded, placebo-controlled trial of intravenous and oral pantoprazole after elective variceal band ligation. Our specific hypotheses were that subjects treated with a proton pump inhibitor following ligation would have fewer and smaller postbanding ulcers and that they would experience less chest pain and odynophagia. Our methods comply with the CONSORT guidelines for reporting clinical trials.[13,14]

Participants. Consecutive subjects presenting for elective variceal band ligation at the procedures unit of the University of North Carolina Hospitals from 2002-2003 were eligible for enrollment. Inclusion criteria were subjects with portal hypertension and varices between the ages of 18 and 80 years who had a history of prior variceal hemorrhage. Prior variceal hemorrhage was defined as bleeding from an esophageal or gastric varix at the time of a prior endoscopy or the presence of large esophageal varices with blood in the stomach and no other recognizable cause of bleeding at a prior endoscopy.[5] Exclusion criteria were: (1) endoscopically confirmed pre-existing esophageal ulcers, (2) ongoing therapy with any anti-acid agent, (3) previous inclusion in the study, (4) previous surgical anti-reflux procedure, including Nissen, Belsey, or Toupet, (5) Barrett's esophagus, (6) history of liver transplantation, (7) pregnancy, and (8) allergy or past adverse reaction to proton pump inhibitors. All subjects were maintained on a beta-blocker during the trial unless they had a contraindication to the use of these compounds. The protocol was approved by the University of North Carolina's Committee on the Protection of Rights of Human Subjects, and each subject was compensated $100 for participation in the trial.

Randomization and Intervention. Subjects were randomized using an opaque envelope technique and were assigned to their groups by a predetermined sequence in the investigational drug pharmacy at the University of North Carolina. Subjects were stratified for randomization into Child-Turcotte-Pugh class A/B or class C to decrease the likelihood that uneven distribution of underlying disease severity would bias the results. Randomization occurred in blocks of four to ensure adequate numbers in each cell for analysis. The patients, the endoscopists, the study personnel, and the statistician were all blinded to the treatment assignments.

Subjects were assigned to one of two interventions. Subjects in the pantoprazole arm received 40 mg pantoprazole intravenously immediately following the banding treatment, then 40 mg pantoprazole orally every morning for an additional 9 days, for a total of 10 days of treatment. Subjects in the control arm received an intravenous bag containing normal saline immediately after the procedure, then an identical placebo tablet every morning for the following 9 days, for a total of 10 days of treatment. In both the pantoprazole and control arms, the intravenous bag was administered with an in-line intravenous filter to maintain blinding, and in both arms the intravenous infusion was administered over a 15-minute period.

Subjects were contacted on day 5 of the study to assess for adverse reactions and compliance to treatment. Ten to 14 days following the initial banding session patients returned to the endoscopy center. At that time pill counts were performed to assess compliance, and the subjects rated their heartburn, regurgitation, chest pain, dysphagia, and odynophagia symptoms using a previously validated questionnaire.[15] Additionally, any history of bleeding complications from the initial banding as well as other adverse events (*e.g.*, possible medication-induced side effects such as diarrhea, nausea, vomiting, and headache) were assessed. All subjects completed a generic quality of life measure (the SF-36) before therapy and again at the termination of therapy.[16,17]

Patients then underwent repeat upper endoscopy. The size and number of any residual banding ulcers were noted and measured using an endoscopic measuring wire designed for endoscopic retrograde cholangiopancreatogram to assess length (Wilson-Cook, Winston-Salem, NC) and an open 7-mm biopsy forceps to approximate width. A postbanding ulcer was defined as a mucosal break in the distal third of the esophagus or the high cardia with any degree of endoscopically appreciable depth. If repeat banding for residual varices was deemed by the endoscopist to be appropriate, it was noted whether the endoscopist assessed it to be safe in the presence of any residual ulceration to perform that banding. Upon discharge from the unit, subjects returned to normal care with follow-up in the hepatology clinic. A final telephone assessment was made 30 days after the second endoscopy to ascertain any adverse outcomes.

Outcome Measures. All measured outcomes were decided *a priori*. The primary outcomes assessed included:

1. the number of esophageal ulcers (adjusted for number of bands placed) identified at follow-up endoscopy;

2. the size of esophageal ulcers identified at follow-up endoscopy after EVL; and
3. dysphagia and chest pain ratings when presenting for follow-up procedure after EVL.

Secondary outcomes included:

1. if repeat variceal ligation was indicated, whether or not the endoscopist assessed it to be safe to proceed;
2. number of bleeding complications noted in study subjects (post-EVL bleeding was defined as either hematemesis or greater than a 3-point drop in hematocrit, accompanied by upper endoscopy demonstrating either a spurting or oozing esophageal ulcer, an adherent clot in the esophagus, or an esophageal ulcer with blood in the stomach and no other pathological condition noted to explain the hemorrhage);
3. serum hematocrit 10 days after EVL; and
4. global SF-36 score.

Power Calculations and Statistics. Sample size calculations were performed using ulcer size, one of the primary outcome measures. Young et al.[9] measured postligation ulcers to have an average diameter of 10.4 mm with a standard deviation of 5.1 mm. For the calculations, we assumed that the control subjects would have these average postligation ulcer dimensions. To show a 50% difference in ulcer diameter between controls and active treatment subjects, and assuming an alpha level of 0.05 and 90% power, a total of 42 evaluable patients were necessary.

Statistical analysis was performed using SAS software (Cary, NC). Univariate statistics demonstrating the means, medians, and interquartile ranges were calculated for both the pantoprazole and control arms. The two patient groups were then compared for Child-Turcotte-Pugh class, age, race, sex, and other demographic and disease-specific variables using chi-square analysis and the Fisher exact test. Ulcer dimensions were converted to estimates of ulcer area by multiplying the reported length of the ulcer by the reported width. Multiple linear regression was performed to assess the number of ulcers present at the follow-up endoscopy, controlling for the number of bands placed at the index endoscopy. Patients taking 80% or more of the study medications were considered compliant with medical therapy. All results reported are noted as means or, when data were not normally distributed, medians, as well as 95% confidence intervals when appropriate. All analyses were performed on an as-randomized, intention-to-treat basis unless noted otherwise.

Results

Forty-four subjects were randomized, 42 of whom successfully completed the entire protocol. No subjects were lost to follow-up. Table 1 describes the key demographic and disease-specific variables of the cohort at study entry. There were no significant differences in key demographic or disease-specific indicators. Pill counts revealed that of the 42 subjects completing the protocol, 40 received all 10 doses of the study medication, 1 took 9 doses, and 1 took 8 doses. Therefore, all subjects completing the protocol made the criteria for compliance. Figure 1 demonstrates the patient flow through the study.

There was no significant difference in the number of bands placed in the pantoprazole and control groups, with a mean of 3.2 bands placed in the treatment group (range, 1-6) and 2.8 bands in the placebo group (range,

Table 1. Demographics and Disease-Specific Data of Subjects in the Pantoprazole and Control Arms

Variable	Control (n = 22)	Pantoprazole (n = 22)	*P* Value*
Sex			
Male	14 (64)	10 (45)	.36
Female	8 (36)	12 (55)	
Age (yr)	50	51	.85
Race			
Caucasian	16 (73)	20 (91)	.11
African American	4 (18)	1 (5)	
Hispanic	2 (9)	0 (0)	
Asian	0 (0)	1 (5)	
Other	0 (0)	0 (0)	
Weight (kg)	81.8	83.6	.79
Child-Turcotte-Pugh score			
A	9 (41)	10 (45)	.85
B	10 (45)	8 (36)	
C	3 (15)	4 (18)	
Gastric varices present			
Yes	2 (10)	5 (24)	.54
No	14 (70)	12 (57)	
Not sure	4 (20)	4 (19)	
Cause of cirrhosis			
Alcohol use	9 (41)	9 (41)	1
HCV	10 (45)	8 (36)	.76
HBV	0 (0)	0 (0)	–
PBC	2 (9)	0 (0)	.49
PSC	0 (0)	0 (0)	–
Other†	8 (36)	8 (36)	1
Actively using alcohol	1 (5)	1 (5)	1
Beta blockade at study entry	12 (55)	15 (68)	.54
Grade of varices			
Grade 1	0 (0)	0 (0)	.75
Grade 2	14 (64)	16 (73)	
Grade 3	8 (36)	6 (27)	
Grade 4	0 (0)	0 (0)	

NOTE. Data represent the number of subjects with the percentage in parentheses, except where indicated. Causes of cirrhosis add up to greater than 100% because some subjects had more than one disease.

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

**P* values were determined using the Fisher exact test for categorical variables and Student *t* test for continuous variables.

†Includes cryptogenic cirrhosis, nonalcoholic fatty liver disease, metabolic disorders such as hereditary hemochromatosis, and drug-induced cirrhosis.

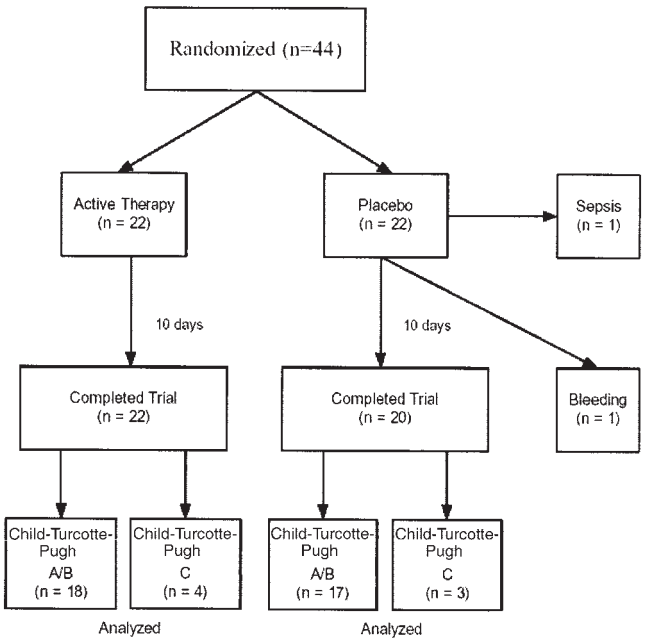

Fig. 1. Flow diagram demonstrating the randomization scheme and safety outcomes of the subjects enrolled. Although 2 subjects in the control group bled during the intervening 10 days of the trial, only 1 did not complete the study.

1-5). Similarly, there was no significant difference in the mean period of follow-up between the first and second endoscopy sessions between the pantoprazole group (11.8 days) and the placebo group (11.9 days).

Primary Outcomes. Table 2 reports the primary outcomes of the study. No significant difference was noted in the number of postbanding ulcers—either when considered in bivariate analysis or when controlled for the number of bands placed—between the pantoprazole and control group. However, ulcer size was significantly larger in the subjects receiving placebo compared with those receiving pantoprazole. On average, ulcers in the placebo group were approximately twice the size of those in the pantoprazole group. Symptom presence and symptom scores for chest pain and dysphagia were not significantly different between the groups, and overall, the rate of symptoms of chest pain and dysphagia were low in both arms when presenting for follow-up endoscopy (less than 15% of the subjects had any of the three symptoms). Table 3 demonstrates the number and size of ulcers in the pantoprazole and control group, stratified by Child-Turcotte-Pugh score. Significantly more and larger ulcers were present in the Child-Turcotte-Pugh class C patients than in the class A and B patients, regardless of treatment assignment.

Secondary Outcomes. At follow-up endoscopy, there were no cases in which the endoscopist felt that the residual ulceration was too extensive to allow repeat banding of any still-existing varices. Similarly, as noted above, only 2 subjects had bleeding episodes in the intervening period between the upper endoscopies, both of whom were in the control arm (*P* value not significant). Mean serum hematocrit levels on follow-up endoscopy were unchanged from baseline levels and not different between the groups (36.4 for control vs. 37.1 for pantoprazole; $P = .69$). Similarly, the global SF-36 scores were not significantly different between the two groups ($P = .79$; complete data not shown).

Safety and Adverse Events. Four serious adverse events occurred during the study or in the following 4 weeks, all to subjects randomized to the control arm ($P = .11$ using the Fisher exact test). Of these events, two were episodes of postbanding hemorrhage that occurred within the 10 days between the first and second banding session. A third was an episode of upper gastrointestinal bleeding that occurred after the treatment period but within 4 weeks of the second upper endoscopy. In all three bleeding events, the source of the bleeding was postbanding ulcers. The fourth event was an episode of sepsis that occurred between the first and second elective banding session. The 2 subjects who did not complete the protocol included the subject who developed sepsis and 1 of the 2 subjects who developed bleeding before the second endoscopy (the second subject bleeding in the period between the two endoscopies underwent the follow-up study endoscopy on day 10 of the study period, at the same time as the investigation for the hemorrhage). Two subjects died of complications of their liver disease during the trial, including the subject who developed sepsis, and one of the two subjects who developed bleeding in the intervening 10 days between banding. Neither subject who died completed the study, and both subjects who died were in the control arm ($P = .49$ using the Fisher exact test).

Discussion

Elective variceal band ligation is a common clinical practice performed with the intent of decreasing subsequent variceal hemorrhage. Although the procedure has

Table 2. Primary Outcome Variables

Variable	Control (n = 20)	Pantoprazole (n = 22)	*P* Value
No. of ulcers, day 10, mean (SE)	2.25 (0.31)	2.18 (0.20)	.85
Ulcer size (mm^2), day 10, mean (SE)	82 (22)	37 (9)	.01
Dysphagia present, day 10, n (%)	1 (5)	3 (14)	.61
Chest pain present, day 10, n (%)	0 (0)	1 (5)	1.0

Table 3. Number of Bands Placed, Number of Subsequent Ulcers, and Ulcer Size, Stratified by Child-Turcotte-Pugh Score

	CTP Score A or B				CTP Score C			
	Control (n = 17)		Pantoprazole (n = 18)		Control (n = 3)		Pantoprazole (n = 4)	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
No. of ulcers	2.18	2	2.06	2	2.67	3	2.75	3
No. of bands placed	3.24	3	2.61	2	3	3	3.5	3.5
Ulcer size, day 10 (mm^2)	74	55	30	25	143	143	65	23

been shown to be effective in decreasing bleeding,[4,18-21] it is associated with side effects of its own, including postligation bleeding, pain from ulceration, dysphagia, and odynophagia.[10,11,22-24]

Few data exist regarding adjuvant therapy for EVL or sclerotherapy. The few groups who have attempted to determine if adjuvant therapy reduces complications have reported mixed results. Nijhawan and Rai[25] randomized 30 subjects undergoing elective EVL to treatment with either sucralfate or placebo. No differences in healing were found between the groups. Conversely, treatment of sclerotherapy ulcers with sucralfate was shown to speed healing in a randomized controlled trial of 45 patients.[26] There are some data to suggest that sclerotherapy ulcers might benefit from treatment with H2 receptor antagonists.[27] However, in a randomized controlled trial of proton pump inhibitors, Garg and colleagues[28] were unable to demonstrate a beneficial effect of omeprazole on postsclerotherapy ulcers. Other series of nonhealing ulcers following sclerotherapy did show that the lesions responded to omeprazole.[29,30] Until the present study, data regarding the effect of proton pump inhibitor therapy specifically in postbanding patients were lacking.

Because gastric acid might contribute to pain and other complications of banding, we hypothesized that treatment with proton pump inhibitors might attenuate the complications of banding. Our results do not unequivocally support this contention. Although we did see a decrease in ulcer size, we did not observe an overall decrease in ulcer number. Similarly, the symptomatology of the two groups at follow-up with respect to dysphagia, chest pain, and heartburn was similar between the groups. It should be noted, however, that few subjects experienced dysphagia, chest pain, or heartburn (9 total for all symptoms in the two groups combined), heightening the possibility of a type 2 statistical error.

We did note an increase in adverse events, including postligation bleeding events associated with the placebo group, but this did not reach statistical significance. This trial was powered only to look at differences in ulcer size, not bleeding events. Because of the relatively low incidence of postbanding hemorrhage (2%-5% in most series),[7,31,32] a study powered to assess differences in bleeding risk would need to be much larger. For instance, assuming that the risk of postbanding hemorrhage is 3%, to assess for a 50% reduction in bleeding with 80% power and an alpha value of .05, a trial with more than 3,000 participants would be necessary. For this reason, we chose to assess ulcer size as a possible predictor of bleeding risk after band ligation. While this supposition seems reasonable, it should be noted that data are not available to substantiate the contention that larger postbanding ulcers hemorrhage more frequently than smaller ones. There are, however, data from other areas of the gastrointestinal tract to suggest that ulcer size is correlated to bleeding rate.[33,34] Our rate of bleeding after elective variceal band ligation (three bleeding episodes in a total of 86 sessions, or 3.5%) is similar to that previously reported by other groups. All three of the bleeding episodes were from postbanding ulcers, and all were in patients treated with placebo.

Although the ulcers in the active treatment group were smaller than those of the control group, the overall number of ulcers, controlled for the number of bands initially placed, did not differ between the groups. This suggests that for the interval between endoscopies in this study, there was insufficient time for complete healing of ulcers. It is possible, given the data shown here, that an interval of longer than 10 days might have demonstrated an overall difference in ulcer number consistent with the greater than 50% reduction in size that was observed. Elective banding to obliteration of visible varices is desirable to decrease the risk of hemorrhage, and it has been suggested that periods of 7 to 14 days between sessions may be optimal to decrease the risk of recurrent hemorrhage.[5,35,36] The presence of residual ulcers in the mucosa at subsequent banding sessions has implications for banding technique. Because ulcers are incompletely healed in that period, our technique involves the placement of bands adjacent to ulcerated areas, attempting to avoid involvement of already ulcerated mucosa. Although it has never been demonstrated, this approach may decrease the risk of bleeding or perforation.

Several strengths of our study deserve mention. The study had rigorously defined, *a priori* outcomes selected. Blinding was complete, and stratification provided equal

spectra of disease in the groups. Monitoring during and after treatment was compulsive, and no subject was lost to follow-up. Compliance was high with the intervention. Several limitations should also be recognized. As noted above, because of the low baseline risk of postligation hemorrhage, we were not able to use this variable as a primary outcome. Second, although the symptom and quality of life tools we used to assess postbanding patients have been widely used in the literature, and have been demonstrated to be responsive to changes in therapy, their validation is primarily in general and/or gastroesophageal reflux disease populations, not specifically in postband ligation groups such as the one studied presently. Although using the available quality of life and symptom severity tools seemed reasonable given what we were measuring, it is possible that these tools are inadequately responsive to show differences in the postbanding patient. Next, we elected to use an initial intravenous dose of pantoprazole to give more immediate onset of action. It is unclear whether these results will be replicable with an initial oral dose of the medication. Finally, we assessed only one dose strength of pantoprazole for this study. It may be that in the short term, more rigorous acid suppression would hasten the healing of ulcers.

In conclusion, this randomized, double-blinded, placebo-controlled trial demonstrated that treatment with 40 mg pantoprazole daily following elective band ligation of varices leads to a 50% reduction in the size of postbanding ulcers at follow-up endoscopy. Given the relatively benign nature of the intervention, treatment of subjects undergoing elective banding with proton pump inhibitors seems advisable based on these data, although further investigation will be necessary to determine if this intervention decreases bleeding episodes and morbidity following EVL.

References

1. Groves AR, Evans JC, Williams JA. Management of internal haemorrhoids by rubber-band ligation. Br J Surg 1971;58:923-924.
2. Carden AB. Rubber ring ligation of internal haemorrhoids. Proc R Soc Med 1970;63(Suppl):112-114.
3. Blaisdell PC. Office ligation of hemorrhoids. JAMA 1968;206:1793.
4. Laine L, el Newihi HM, Migikovsky B, Sloane R, Garcia F. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. Ann Intern Med 1993;119:1-7.
5. Jalan R, Hayes PC. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. British Society of Gastroenterology. Gut 2000;46(Suppl 3-4):III1-III15.
6. Stiegmann GV, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saeed ZA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med 1992;326:1527-1532.
7. Gimson AE, Ramage JK, Panos MZ, Hayllar K, Harrison PM, Williams R, et al. Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices. Lancet 1993;342:391-394.
8. Hou MC, Lin HC, Lee FY, Chang FY, Lee SD. Recurrence of esophageal varices following endoscopic treatment and its impact on rebleeding: comparison of sclerotherapy and ligation. J Hepatol 2000;32:202-208.
9. Young MF, Sanowski RA, Rasche R. Comparison and characterization of ulcerations induced by endoscopic ligation of esophageal varices versus endoscopic sclerotherapy. Gastrointest Endosc 1993;39:119-122.
10. Schoonbroodt D, Zipf A, Jung M. Local necrosis and fatal perforation of oesophagus after endoscopic ligation. Lancet 1994;344:1365.
11. Marks RD, Arnold MD, Baron TH. Gross and microscopic findings in the human esophagus after esophageal variceal band ligation: a postmortem analysis. Am J Gastroenterol 1993;88:272-274.
12. Cotton P, Williams CB. Practical Gastrointestinal Endoscopy. Cambridge, MA: Blackwell Science, 1996.
13. Rennie D. How to report randomized controlled trials. The CONSORT statement. JAMA 1996;276:649.
14. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA 1996;276:637-639.
15. Locke GR, Talley NJ, Weaver AL, Zinsmeister AR. A new questionnaire for gastroesophageal reflux disease. Mayo Clin Proc 1994;69:539-547.
16. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36), I: conceptual framework and item selection. Med Care 1992;30:473-483.
17. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993;2:217-227.
18. Sarin SK, Guptan RK, Jain AK, Sundaram KR. A randomized controlled trial of endoscopic variceal band ligation for primary prophylaxis of variceal bleeding. Eur J Gastroenterol Hepatol 1996;8:337-342.
19. Baroncini D, Milandri GL, Borioni D, Piemontese A, Cennamo V, Billi P, et al. A prospective randomized trial of sclerotherapy versus ligation in the elective treatment of bleeding esophageal varices. Endoscopy 1997;29:235-240.
20. Albillos A, Calleja JL. Endoscopic variceal ligation in prophylaxis of first variceal bleeding in cirrhotic patients with high-risk esophageal varices. Gastrointest Endosc 1998;47:202-204.
21. Svoboda P, Kantorova I, Ochmann J, Kozumplik L, Marsova J. A prospective randomized controlled trial of sclerotherapy vs ligation in the prophylactic treatment of high-risk esophageal varices. Surg Endosc 1999;13:580-584.
22. Toyoda H, Fukuda Y, Katano Y, Ebata M, Nagano K, Morita K, et al. Fatal bleeding from a residual vein at the esophageal ulcer base after successful endoscopic variceal ligation. J Clin Gastroenterol 2001;32:158-160.
23. Van Vlierberghe H, De Vos M, Hautekeete M, Elewaut A. Severe bleeding following endoscopic variceal ligation: should EVL be avoided in Child C patients? Acta Gastroenterol Belg 1999;62:175-177.
24. Chen WC, Hou MC, Lin HC, Chang FY, Lee SD. Symptomatic esophageal stricture after endoscopic variceal ligation—success of endoscopic balloon dilation. Zhonghua Yi Xue Za Zhi 2000;63:144-147.
25. Nijhawan S, Rai RR. Does post-ligation oesophageal ulcer healing require treatment? Lancet 1994;343:116-117.
26. Yang WG, Hou MC, Lin HC, Kuo BI, Lee FY, Chang FY, et al. Effect of sucralfate granules in suspension on endoscopic variceal sclerotherapy induced ulcer: analysis of the factors determining ulcer healing. J Gastroenterol Hepatol 1998;13:225-231.
27. Tamura S, Shiozaki H, Kobayashi K, Yano H, Tahara H, Miyata M, et al. Prospective randomized study on the effect of ranitidine against injection ulcer after endoscopic injection sclerotherapy for esophageal varices. Am J Gastroenterol 1991;86:477-480.
28. Garg PK, Sidhu SS, Bhargava DK. Role of omeprazole in prevention and treatment of postendoscopic variceal sclerotherapy esophageal complications: double-blind randomized study. Dig Dis Sci 1995;40:1569-1574.
29. Gimson A, Polson R, Westaby D, Williams R. Omeprazole in the management of intractable esophageal ulceration following injection sclerotherapy. Gastroenterology 1990;99:1829-1831.
30. Shephard H, Barkin JS. Omeprazole heals mucosal ulcers associated with endoscopic injection sclerotherapy. Gastrointest Endosc 1993;39:474-475.

31. Laine L, Stein C, Sharma V. Randomized comparison of ligation versus ligation plus sclerotherapy in patients with bleeding esophageal varices. Gastroenterology 1996;110:529-533.
32. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: a meta-analysis. Ann Intern Med 1995;123:280-287.
33. Guglielmi A, Ruzzenente A, Sandri M, Kind R, Lombardo F, Rodella L, et al. Risk assessment and prediction of rebleeding in bleeding gastroduodenal ulcer. Endoscopy 2002;34:778-786.
34. Paspatis GA, Charoniti I, Papanikolaou N, Vardas E, Chlouverakis G. A prospective, randomized comparison of 10-Fr versus 7-Fr bipolar electrocoagulation catheter in combination with adrenaline injection in the endoscopic treatment of bleeding peptic ulcers. Am J Gastroenterol 2003;98: 2192-2197.
35. Avgerinos A, Armonis A, Manolakopoulos S, Poulianos G, Rekoumis G, Sgourou A, et al. Endoscopic sclerotherapy versus variceal ligation in the long-term management of patients with cirrhosis after variceal bleeding: a prospective randomized study. J Hepatol 1997;26:1034-1041.
36. De BK, Ghoshal UC, Das T, Santra A, Biswas PK. Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: preliminary report of a randomized controlled trial. J Gastroenterol Hepatol 1999;4: 220-224.