Variceal Rebleeding and Recurrence After Endoscopic Injection Sclerotherapy

A Prospective Evaluation in 204 Patients

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Hypothesis: Eradication of esophageal varices by repeated injection sclerotherapy and maintenance of eradication using continued surveillance endoscopy may reduce recurrent variceal bleeding and death from esophageal varices.

Design: A prospective study of consecutive adult patients with endoscopically proved esophageal variceal bleeding.

Setting: A tertiary care university hospital in a metropolitan area.

Patients: Two hundred four patients (127 men and 77 women; mean age, 50.1 years; age range, 16-82 years) underwent 993 emergency and elective variceal endoscopic injection treatments with 5% ethanolamine oleate during 1992 endoscopy sessions. Most (166 [81.4%]) had cirrhosis, mainly due to alcohol abuse (131 [78.9%]). The number of patients with each modified Pugh-Child risk grade was as follows: A, 30; B, 91; and C, 83. (The modified Pugh-Child classification comprises ascites, encephalopathy, serum albumin and bilirubin levels, and prothrombin time. Each variable is given a value of 1 to 3 with increasing impairment of liver function. Addition of the values leads to the Pugh-Child risk grades for each patient, with 5 and 6 giving grade A; 7 through 9, grade B; and 10 through 15, grade C, respectively.)

Results: Ninety-five patients (46.6%) rebled at a median of 17 days (range, 0-2583 days). Seventy-four patients (36.3%) had a total of 112 further bleeding episodes before eradication of varices. Varices were eradicated in 99 (87.6%) of 113 patients who survived longer than 3 months after a median of 5 injections and remained eradicated in 43 (mean follow-up after eradication, 38 months; range, 4-125 months). Rebleeding was markedly reduced after eradication of varices. Varices recurred in 56 patients, of whom only 10 rebled from recurrent esophageal varices. Cumulative survival by life table analysis was 55%, 41%, and 30% at 1, 3, and 5 years, respectively. One hundred thirty-seven patients (67.2%) died during follow-up. Liver failure was the most common cause of death. Minor complications (mucosal ulceration) occurred in 105 patients. Major complications, including a localized injection site leak (n=9), esophageal stenosis (n=25), and esophageal perforation (n=5), occurred in 39 patients.

Conclusions: Repeated injection sclerotherapy eradicated esophageal varices in most long-term patients. Complications related to injection sclerotherapy were mostly minor. Complete eradication of varices reduced rebleeding and death from esophageal varices.
PATIENTS AND METHODS

Consecutive adult patients with endoscopically proved esophageal variceal bleeding, admitted to a specialized surgical unit with a particular interest in portal hypertension in Groote Schuur Hospital, Cape Town, South Africa, between July 1, 1984, and December 31, 1989, were assessed. All patients included in the study were referred either with active variceal bleeding or after an endoscopically proved variceal bleed, and received emergency sclerotherapy. All injection treatments, emergency and subsequent elective injections, were analyzed to assess the role of fiberoptic sclerotherapy in long-term management. All patients were studied prospectively, and the data were entered in a computer program by a research assistant. During the 66-month study period, 218 consecutive adult patients were treated for esophageal variceal bleeding. Two hundred four patients were examined. Fourteen patients were excluded from the study analysis, 13 of whom underwent esophageal transection and gastric devascularization as part of a randomized trial after initial control of acute variceal bleeding by sclerotherapy and 1 who underwent liver transplantation. Data were analyzed in December 1997 to allow an 8-year follow-up period. The overall incidence of rebleeding after initiating sclerotherapy was determined in all patients, as was the incidence of bleeding before and after variceal eradication, to assess the influence of achieving the end point (variceal eradication) in the sclerotherapy program.

TECHNIQUE OF SCLEROTHERAPY

A standard IST technique was used. Diagnostic endoscopy and IST were performed using a fiberoptic endoscope (model GIF 1T20 or K10; Olympus Corp, Lake Success, NY) and intravenous sedation with midazolam hydrochloride. The sclerosant, 5% ethanolamine oleate, was injected using a combined intravariceal and paravariceal technique. A maximum total volume of 25 mL of sclerosant was injected at any one endoscopy session for control of acute variceal bleeding or when large varices (grade 4 or 5) were encountered during elective sclerotherapy. The purely intravariceal technique, with smaller total volumes of sclerosant, was used for elective IST when varices were grade 3 or less in size. The initial session and the second sclerotherapy session (performed a week later) were performed during the index hospital admission. Subsequent sclerotherapy was undertaken at 1-week intervals on an outpatient basis until all the varices were eradicated. After variceal obliteration, surveillance endoscopy was performed at 3 and 6 months and then annually to identify patients in whom varices had recurred. Repeated injection sclerotherapy was performed whenever residual or recurrent varices were present on endoscopy.

REBLEEDING

Recurrent bleeding was defined as any episode of upper gastrointestinal tract bleeding that occurred after the first sclerotherapy session or subsequently between scheduled treatment sessions. Any patient who rebled after leaving the hospital was urgently referred to our variceal unit; all such bleeding episodes were investigated by means of emergency endoscopy, undertaken promptly after admission. Rebleeding was treated according to endoscopic findings. Additional sclerotherapy was undertaken if bleeding was the result of patent residual or recurrent varices. Other sources of bleeding, such as peptic ulceration, gastric varices, erosive gastritis, or portal hypertensive gastropathy, were included in the definition of rebleeding. Eradication of varices was defined as the absence of varices on subsequent endoscopic examination during follow-up visits.

SURVIVAL ANALYSIS

The effects of the cause of the liver disease and the modified Pugh-Child risk grading on survival were determined using univariate analysis of survival according to the Kaplan-Meier method. The Wilcoxon rank sum test was used to assess significance.

RESULTS

The 204 patients examined in this study consisted of 127 men and 77 women (mean age, 50.1 years; age range, 16-82 years) who underwent 993 emergency and elective injection treatments with 5% ethanolamine oleate during 1992 endoscopy sessions. The cause of the portal hypertension is shown in Table 1. Most (166 [81.4%]) had cirrhosis, mainly due to alcohol abuse (131 [78.9%]). When assessed on first admission, 30 patients had Pugh-Child grade A; 91, grade B; and 83, grade C. The modified Pugh-Child classification comprises ascites, encephalopathy, serum albumin and bilirubin levels, and prothrombin time. Each variable is given a value of 1 to 3 with increasing impairment of liver function. Addition of the values leads to the Pugh-Child risk grades for each patient, with 5 and 6 giving grade A; 7 through 9, grade B; and 10 through 13, grade C, respectively.

OVERALL RECURRENT BLEEDING

Of the 204 patients, 95 (46.6%) rebled at a median of 17 days (range, 0-2583 days) during the study period. Seventy-one patients bled from esophageal varices and 24 from injection site ulceration, gastric varices, portal hy-
pertension gastropathy, or nonvariceal gastric or duodenal causes.

RECURRENT BLEEDING BEFORE VARICEAL ERADICATION

Rebleeding occurred in 74 (36.3%) of the 204 patients before eradication either during their index admission or subsequent to discharge. These 74 patients had a total of 112 bleeds during 103 subsequent admissions before the varices were eradicated. The number of rebleeds (112 episodes) before eradication of varices during 5386 patient-months was calculated at 0.02 per patient-months of follow-up. Sixty-one patients bled from varices, and 13 bled from nonvariceal sources. The 61 patients had 86 variceal bleeds that were successfully treated with short-term emergency IST on 61 occasions. The remaining 25 patients with variceal bleeds were not treated by short-term sclerotherapy and were managed with esophageal balloon tamponade followed by subsequent IST. Thirteen patients had 26 bleeding episodes from nonvariceal causes. Nine bleeding episodes were due to bleeding from esophageal injection-induced ulceration and were settled with conservative treatment, which included blood transfusions, intravenous vasopressin, and oral sucralfate. The remaining 17 bleeding episodes were from gastric varices, gastric erosions, portal hypertensive gastropathy, gastric ulceration, or duodenal ulceration.

ERADICATION OF VARICES

Eradication and subsequent recurrence of esophageal varices after sclerotherapy were assessed in 113 of the 204 patients who survived and who were followed up for more than 3 months (Figure 1). Of the remaining 91 patients, 64 died within 3 months of enrolling into the study and 27 did not complete the 3-month follow-up. Six of these 27 patients moved overseas, 19 lived geographically distant from our center and did not attend regularly, and 2 refused further treatment.

Esophageal varices were eradicated in 99 of the 113 patients after a median of 5 injections during a mean of 8.0 months (median, 5 months; range, 1-42 months) (Table 2). Esophageal varices remained eradicated in 43 patients (mean follow-up from eradication, 38 months; median, 29 months; range, 4-125 months). Of these 43 patients whose varices did not recur, 23 died with their varices eradicated (mean follow-up from eradication, 38 months; range, 4-100 months) and 20 were alive at the end of the study without varices (mean, 50 months; median, 38 months; range, 3-125 months) after eradication (Figure 1). The 14 patients whose varices were not eradicated received a mean of 4 injections during a mean of 6.1 months. Nine of the 14 patients died of progressive liver failure before the varices could be eradicated. Two patients underwent elective surgery (esophageal transection and devascularization in 1 and the placement of a distal splenorenal shunt in another). Three patients declined regular long-term follow-up and further injection therapy.

Varices were eradicated in 11 of the 13 patients with primary extrahepatic portal venous obstruction after a mean of 5 injections during a mean of 11 months in the eradicated patients. In 64 of the 74 patients with alcohol-induced cirrhosis who survived and were followed up for more than 3 months, varices were eradicated, requiring a mean of 6 injections during a mean of 9.7 months. Of the 19 patients with non-alcohol-induced cirrhosis who survived for more than 3 months, varices were eradicated in 17 after 6 injections during 4.3 months. Twenty-one of the 56 patients with recurrence of esophageal varices after eradication presented with bleeding, which was due to variceal bleeding in 10 patients (Figure 1). This occurred after a mean of 16.1 months. When varices recurred, they were usually small and easily reeradicated by sclerotherapy.

RECURRENT BLEEDING AFTER VARICEAL ERADICATION

Twenty-five patients rebled after eradication of esophageal varices. In 4 patients, the varices remained obliterated and the sites of bleeding were gastric varices, gastric erosions, and rectal varices; the site was not found in 1 patient. Twenty-one patients had recurrent varices and rebled, but of these only 10 rebled from esophageal varices (Figure 1). These 10 patients were treated with

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Table 1. Causes of Portal Hypertension in 204 Patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>Total No. of Patients</th>
<th>No. of Patients Followed Up &gt; 90 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td></td>
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<tr>
<td>Alcoholic</td>
<td>131</td>
<td>74</td>
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<tr>
<td>Viral hepatitis type B positive</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>2</td>
<td>2</td>
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<td>Unknown</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
<td>113</td>
</tr>
</tbody>
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Table 2

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>113</td>
</tr>
<tr>
<td>Esophageal varices in 10 Patients</td>
<td>14 (12.4%)</td>
</tr>
<tr>
<td>Other Causes, in 11 Patients</td>
<td>56 (56.6%)</td>
</tr>
<tr>
<td>Alive</td>
<td>43 (43.4%)</td>
</tr>
<tr>
<td>Dead</td>
<td>21 (21.7%)</td>
</tr>
<tr>
<td>No Bleeding</td>
<td>35 (62.5%)</td>
</tr>
<tr>
<td>Survival &gt; 3 mo</td>
<td>113 Patients</td>
</tr>
<tr>
<td>Survival &lt; 3 mo (n=64)</td>
<td>91 Patients</td>
</tr>
<tr>
<td>Varices Eradicated</td>
<td>99 (87.6%)</td>
</tr>
<tr>
<td>Varices Not Eradicated</td>
<td>14 (12.4%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>56 (56.6%)</td>
</tr>
<tr>
<td>No Recurrence</td>
<td>43 (43.4%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>21 (21.7%)</td>
</tr>
<tr>
<td>No Bleeding</td>
<td>35 (62.5%)</td>
</tr>
</tbody>
</table>

Figure 1. Eradication and recurrence of esophageal varices.
Table 2. Number of Injections and Time to Eradication of Varices

<table>
<thead>
<tr>
<th>Pugh-Child Grade*</th>
<th>Total No. of Patients</th>
<th>Patients Followed Up &gt;90 d†‡</th>
<th>Patients With Eradicated Varices†§</th>
<th>No. of Injections[</th>
<th>Time to Eradicate Varices, mo]</th>
<th>Patients With Recurrent Varices†¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>23 (76.7)</td>
<td>20 (87.0)</td>
<td>5 (1-11)</td>
<td>7.4 (1-31)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>B</td>
<td>91</td>
<td>64 (70.3)</td>
<td>58 (90.6)</td>
<td>5 (1-13)</td>
<td>8.5 (1-42)</td>
<td>37 (64)</td>
</tr>
<tr>
<td>C</td>
<td>83</td>
<td>26 (31.3)</td>
<td>21 (80.8)</td>
<td>5 (2-14)</td>
<td>7.4 (1-25)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
<td>113 (55.4)</td>
<td>99 (87.6)</td>
<td>5 (1-14)</td>
<td>8.0 (1-42)</td>
<td>64 (65)</td>
</tr>
</tbody>
</table>

* The modified Pugh-Child classification comprises ascites, encephalopathy, serum albumin and bilirubin levels, and prothrombin time. Each variable is given a value of 1 to 3 with increasing impairment of liver function. Addition of the values leads to the Pugh-Child risk grades for each patient with 5 and 6 giving grade A, 7 through 9 grade B, and 10 through 15 grade C, respectively.
† Data are given as number (percentage) of patients.
‡ The denominator used was the total number of patients in that row.
§ The denominator used was the number of patients followed up for longer than 90 days in that row.
[ Data are given as mean (range).
¶ The denominator used was the number of patients with eradicated varices in that row.

Table 3. Complications in 204 Patients (993 Sclerotherapy Treatments)*

<table>
<thead>
<tr>
<th>Type of Complication</th>
<th>Complications per Sclerotherapy Treatment</th>
<th>Complications per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal ulceration</td>
<td>391 (39.4)</td>
<td>144 (70.6)</td>
</tr>
<tr>
<td>Injection site leak</td>
<td>9 (0.9)†‡</td>
<td>9 (4.4)†‡</td>
</tr>
<tr>
<td>Stricture</td>
<td>25 (2.5)†‡</td>
<td>25 (12.3)†‡</td>
</tr>
<tr>
<td>Perforation</td>
<td>5 (0.5)†‡</td>
<td>5 (2.5)†‡</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage).
† Included in the esophageal ulceration group.

repeated sclerotherapy, and the varices were eradicated after a mean of 2.4 injections (range, 1-4 injections). In the remaining 11 patients, bleeding was due to gastric varices, portal hypertensive gastropathy, gastric or duodenal erosions, or gastric ulcer; in 3 patients, the exact site of bleeding could not be determined with certainty during endoscopy.

ESOPHAGEAL COMPLICATIONS

The 204 patients received a total of 993 emergency and elective injection treatments during 1992 endoscopy sessions. Minor complications of sclerotherapy were common and consisted of transient fever, pleural effusion, and pulmonary atelectasis. A total of 391 complications occurred in 144 patients (Table 3). Thus, 70.6% of the patients had 1 or more complications and 1 in 2.5 sclerotherapy treatments was followed by a complication.

Esophageal mucosal ulceration at the injection site was found at follow-up endoscopy on 391 occasions in 144 patients. Subsequent sclerotherapy was delayed only in patients who had mucosal ulceration in greater than 1 quadrant of the esophageal circumference. One patient had major bleeding, and only this patient died as a consequence of esophageal ulceration.

A contained injection site leak occurred on 9 occasions in 9 patients and was treated with intravenous antibiotics and fine-bore silastic nasogastric tube feeding. Although the leak settled on conservative treatment in all instances, repeated sclerotherapy was deferred for 1 month until complete healing had occurred. An esophageal stricture at the injection site occurred in 25 patients after sclerotherapy. Fifteen patients required esophageal dilation, with complete relief of symptoms after a mean of 4 dilation sessions (range, 1-7 sessions).

Perforation of the esophagus occurred in 5 patients as a consequence of injection for control of acute bleeding. Four patients underwent thoracotomy and drainage of the mediastinum, and 1 was managed conservatively. Four of the 5 patients died, including the patient treated conservatively (who died of liver failure). The surviving patient underwent placement of a Warren distal splenorenal shunt for persistent varices 4 months after the perforation and remains well 8½ years later, with eradicated varices on follow-up esophagoscopy.

SURVIVAL ANALYSIS

The cumulative survival of the 204 patients, by life table analysis, is shown in Figure 2. The probability of surviving 6 months was 60%, and the 1-year survival was 55%. Cumulative survival was 41% at 3 years and 30% at 5 years. The effect of the initial admission Pugh-Child grading on survival is shown in Figure 2. The survival for patients with a Pugh-Child grade of A was significantly better than for those with a grade of B (P<.001), and the survival for those with a grade of B was significantly better than for those with a grade of C (P<.001). Patients with extrahepatic portal venous obstruction (Figure 3) fared significantly better than patients with cirrhosis (P<.03).

CAUSES OF DEATH

One hundred thirty-seven (67.2%) of the 204 patients died during the study. Liver failure was the major cause of death in 66 patients, and hepatorenal failure was the major cause in 30 patients. Seven patients died of pneumonia, 13 of multiorgan failure associated with bleeding varices, and 4 of bleeding from other sites (spleenic vein, 2; rectal varices, 1; and esophageal ulcer following...
injection, 1). Seventeen patients died of other causes, including carcinoma in 11 (lung, 2; pancreas, 2; hepatoma, 4; stomach, 1; pharynx, 1; and angiosarcoma of the liver, 1); myocardial infarction, 2; cerebrovascular accident, 1; injury from a motor vehicle crash, 1; perforated gastric ulcer, 1; and septicemia following hip surgery, 1.

**COMMENT**

Despite the widespread use of endoscopic sclerotherapy for the treatment of bleeding esophageal varices and a plethora of published studies, accurate long-term data detailing recurrence, rebleeding after eradication, or the need for prolonged endoscopic surveillance are scant.33-36 The lack of a specific, predetermined end point when using sclerotherapy31,38,39 and the technical differences, including the type, volume, and concentration of sclerosant40-42 make the esophageal segment injected, the technique of injection,43-45 the repeated injection schedule,46,47 and the intensity of subsequent endoscopic surveillance,48 have complicated the comparison of treatments from different institutions.33-39 Previous studies40,42 of repeated sclerotherapy have also been restricted by small numbers of patients and limited follow-up.

In this prospective study, the long-term efficacy of IST was evaluated by using the specific end points of recurrent bleeding, variceal eradication, and survival in consecutive patients at a single center by an experienced team of surgical endoscopists (J.E.J.K., and P.C.B.). The most important limitation of long-term IST is the high incidence of rebleeding, which is a particular feature of the early phase after therapy has begun.31,24,28 The most common source of recurrent bleeding before variceal eradication was from residual patent varices that occurred in 36.3% of our patients.

Urgent endoscopy is essential since 82.4% of patients with recurrent bleeding, varices are the source and are optimally treated by repeated sclerotherapy, which was effective in 61 of 86 variceal rebleeds. In 17.6% of patients, a nonvariceal source of bleeding was identified. Since most patients in this study with recurrent variceal bleeding responded to continued sclerotherapy with ultimate eradication, the onset of recurrent bleeding does not indicate that sclerotherapy has failed. While *sclerotherapy failure* during the index admission for acute bleeding has been defined as continued bleeding despite 2 adequate sclerotherapy sessions,53 a universally acceptable definition of long-term sclerotherapy failure has been more elusive.20 Recurrent bleeding from causes for which continued injection treatments are contraindicated are true failures of sclerotherapy and include bleeding from deep ulcers at the injection site, complex fundal gastric varices, portal hypertensive gastropathy, or continued life-threatening bleeds from patent residual esophageal varices despite sclerotherapy.54

Repeated sclerotherapy successfully eradicated esophageal varices after a median of 5 sclerotherapy sessions in 99 of the 113 patients followed up for more than 90 days. Overall, the varices remained eradicated for a mean of 38 months. Although new varices formed following initial obliteration in 53 of the 100 patients, this was associated with rebleeding from varices in only 8 patients. The number of sclerotherapy sessions required to achieve variceal obliteration has varied considerably within reported series and between centers. While there is some evidence to suggest that the technique of IST might affect the number of sessions necessary to achieve obliteration,27,41 this alone does not explain the substantial differences found between patients. Recent studies55,56 of the lower esophagus have clarified the detailed anatomical features of the critical zone of bleeding and may provide a clue for the early success of injection and an explanation for the frequent recurrence of varices after eradication by sclerotherapy. Such differences might be attrib-
uted to the variation in venous anatomical features of the lower esophagus, and in particular to the presence of perforating veins communicating between the intrinsic and paraesophageal vessels. The importance of perforating vessels has been confirmed by demonstrating the need for an increased number of sclerotherapy sessions in those in whom perforating vessels had been demonstrated. Patients with paraesophageal varices required more treatment sessions, more sclerosant, and longer periods to achieve variceal obliteration. In addition, varices reappeared at an earlier stage in patients in whom esophageal perforating vessels had been demonstrated.

There is neither uniformity nor universal agreement regarding the definition or classification of complications that occur after IST. Consequently, the incidence varies widely in reported studies. Detailed comparisons of complication rates between centers are hampered by variations in patient population, type and severity of liver disease, and different injection techniques used and are higher when carefully documented in prospective studies. The present study evaluated the complications occurring in 204 patients undergoing emergency and elective sclerotherapy. Complications were frequent, but were mostly minor, occurring in a quarter of all sclerotherapy treatments and in more than half of patients. Asymptomatic esophageal ulceration at the injection site was the most common complication and was detected at follow-up endoscopy. Ulceration was usually of little consequence in the overall management of the patient, but occasionally subsequent sclerotherapy had to be delayed. Ulcers are generally considered an inevitable temporary consequence of the sclerosant, occurring after frequent or large-volume injections. In most patients in this study, mucosal ulceration healed without sequelae. Our present policy is to use lower volumes of sclerosant as varices decrease in size in an attempt to reduce the extent of ulceration. When ulceration involves more than one quadrant of the esophageal circumference, further injection has been delayed until healing has occurred to prevent esophageal stricture. Injection site leaks occurred in 9 patients and were successfully treated by conservative measures, although subsequent sclerotherapy was delayed. Other serious complications included esophageal stenosis and perforation. Esophageal stenosis was significant in 15 of the 25 patients with this complication, and all responded to dilation. Perforation of the esophagus in this study was confined to emergency injection for recurrent bleeding and had a high associated mortality.

Variceal ligation is the other major endoscopic option in the treatment of patients with bleeding esophageal varices. Three meta-analyses have evaluated the randomized trials that compared endoscopic ligation with sclerotherapy in patients with bleeding esophageal varices. Those who underwent ligation therapy had less bleeding and a lower mortality. Esophageal strictures occurred less frequently with ligation, and the number of endoscopic treatment sessions required to achieve variceal obliteration was lower with ligation than with sclerotherapy. In a subsequent study, Gralnek et al evaluated the direct costs of health care use and cost-effectiveness of endoscopic IST compared with EVL in the prevention of variceal rebleeding and patient survival at 1-year follow-up. Treatment groups were similar in incidence of variceal rebleeding (41.9% vs 42.9%), incidence of variceal obliteration (41.9% vs 40.0%), length of hospital days, number of blood transfusions, whether shunts were required, and length of survival (71.0% vs 60.0%). There were significantly more treatment failures for active bleeding using EVL (42% vs 0%; P = .03) and more esophageal stricture formation in the endoscopic IST–treated patients (19.4% vs 2.9%; P = .03). The median total direct cost outcomes were similar between groups (EVL vs endoscopic IST, $9696 vs $13197; P = .46). Endoscopic variceal ligation and endoscopic IST had a similar cost per variceal rebleeding prevented ($28678 vs $29093) and cost per survival ($27313 vs $23804). In the subgroup of active bleeds, endoscopic IST had a substantially lower cost per survival ($28523 vs $51696).

Despite the overall better results achieved with EVL, repeated sclerotherapy, by virtue of its simplicity and availability, remains an important endoscopic treatment option, especially for control of acute bleeding and in the long-term treatment of variceal bleeding when varices are small. Several important problems related to repeated sclerotherapy in long-term management remain. Recurrent variceal bleeding remains the most limiting aspect of long-term sclerotherapy. While the risk diminishes with time as the variceal channels are obliterated, some recurrent bleeds are fatal or contribute to deaths from liver failure. Any protocol for long-term endoscopic management of variceal hemorrhage requires a firm definition of treatment failure, which allows alternative treatment options to be instigated. That such a definition is difficult to formulate is reflected in the major discrepancies in the proportion of treatment failures in the larger controlled trials. Long-term sclerotherapy also requires lifelong follow-up with repeated injections because varices recur in time. Surviving patients, however, place an increasing burden on hospital resources, even when sclerotherapy (or variceal ligation) is performed on an outpatient basis.

Our long-term management policy based on the data given recommends that patients undergo weekly variceal endoscopic therapy to achieve the end point of variceal eradication. After eradication of the varices, patients are followed up with surveillance endoscopy at 6-month intervals and, if varices recur, a further program of endotherapy is instituted again. Our present endoscopic management has been influenced by the introduction of EVL techniques that have resulted in safer and quicker variceal eradication, although recurrence rates may be higher than those for sclerotherapy. Although the combination of initial ligation and sclerotherapy together (synchronous therapy) has not proved beneficial, the use of variceal banding when varices are large followed subsequently by sclerotherapy (sequential therapy) when varices are smaller (and more difficult to band adequately) may facilitate earlier eradication and prevention of recurrence of varices. However, the pro-
hibitive cost of disposable variceal banding equipment ($200 per unit) limits its universal use, particularly in developing countries with limited fiscal and health care resources.

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Impact of Helicobacter pylori Infection on Gastric Cancer Incidence in a General Japanese Population: The Hisayama Study

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Background: Several nested case-control studies have reported the potentially causal relationship between Helicobacter pylori infection and the development of gastric cancer. However, there has been no prospective study evaluating this issue. The purpose of this study is to examine the impact of H pylori infection on gastric cancer occurrence in a general Japanese population (Hisayama, Japan) stratified according to sex, using a prospective study design.

Methods: A total of 2602 subjects aged 40 years or older (1070 men; mean age, 57 years; 1532 women; mean age, 59 years) without a history of gastrectomy or gastric cancer were classified according to the status of the serum IgG antibodies to H pylori and observed prospectively for 9 years from 1988.

Results: Infection of H pylori was more common in men (71.5%) than in women (62.5%; P < .001). The age-adjusted incidence of gastric cancer for men (5.3 per 1000 person-years) was 4-fold higher than that for women (1.3; P < .001). In men, the age-adjusted incidence of gastric cancer was significantly higher in the subjects with H pylori infection than in those without it (6.2 vs 2.5; relative risk, 2.59 [95% confidence interval, 1.03-6.50]); whereas no significant difference was observed in women (1.2 vs 1.1; relative risk, 0.99 [95% confidence interval, 0.36-2.68]). These results were similar even after controlling for other risk factors in multivariate analysis. It was estimated that 40.1% of gastric cancers for men in this cohort were attributable to H pylori infection.

Conclusion: A significant relationship exists between infection with H pylori and subsequent occurrence of gastric cancer for men but not for women in this Japanese population.

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