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## EFFECT OF INTRAVENOUS OMEPRAZOLE ON RECURRENT BLEEDING AFTER ENDOSCOPIC TREATMENT OF BLEEDING PEPTIC ULCERS

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### ABSTRACT

**Background** After endoscopic treatment of bleeding peptic ulcers, bleeding recurs in 15 to 20 percent of patients.

**Methods** We assessed whether the use of a high dose of a proton-pump inhibitor would reduce the frequency of recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. Patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels were treated with an epinephrine injection followed by thermocoagulation. After hemostasis had been achieved, they were randomly assigned in a double-blind fashion to receive omeprazole (given as a bolus intravenous injection of 80 mg followed by an infusion of 8 mg per hour for 72 hours) or placebo. After the infusion, all patients were given 20 mg of omeprazole orally per day for eight weeks. The primary end point was recurrent bleeding within 30 days after endoscopy.

**Results** We enrolled 240 patients, 120 in each group. Bleeding recurred within 30 days in 8 patients (6.7 percent) in the omeprazole group, as compared with 27 (22.5 percent) in the placebo group (hazard ratio, 3.9; 95 percent confidence interval, 1.7 to 9.0). Most episodes of recurrent bleeding occurred during the first three days, which made up the infusion period (5 in the omeprazole group and 24 in the placebo group,  $P < 0.001$ ). Three patients in the omeprazole group and nine in the placebo group underwent surgery ( $P = 0.14$ ). Five patients (4.2 percent) in the omeprazole group and 12 (10 percent) in the placebo group died within 30 days after endoscopy ( $P = 0.13$ ).

**Conclusions** After endoscopic treatment of bleeding peptic ulcers, a high-dose infusion of omeprazole substantially reduces the risk of recurrent bleeding. (N Engl J Med 2000;343:310-6.)

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**E**NDOSCOPIC treatment is effective for bleeding peptic ulcers, but bleeding recurs in 15 to 20 percent of patients. The mortality rate in these patients is high. In vitro studies have shown that a high intragastric pH could facilitate platelet aggregation.<sup>1</sup> Thus, inhibition of gastric acid to maintain a neutral pH should stabilize clots and prevent recurrent bleeding. However, the role of acid suppression in the management of bleeding peptic ulcers, particularly after endoscopic treatment, remains unclear.

Evidence of the effectiveness of histamine H<sub>2</sub>-receptor antagonists in bleeding peptic ulcers is conflicting. In a meta-analysis of 27 randomized trials, Collins and Langman concluded that the use of these antagonists reduced the rate of continued bleeding, the need for surgery, and the risk of death only among patients with gastric ulcers.<sup>2</sup> In a multicenter trial that compared famotidine infusion with placebo infusion in 1005 patients, the rate of recurrent bleeding was similar in the two groups.<sup>3</sup>

In vivo studies have shown that a regimen that includes high doses of a proton-pump inhibitor maintains intragastric pH at a nearly neutral level<sup>4,5</sup> and inhibits acid production more effectively than does an infusion of H<sub>2</sub>-receptor antagonists. Furthermore, tolerance of the antisecretory effect of H<sub>2</sub>-receptor antagonists, with loss of pH control, develops during the 72-hour period of infusion.<sup>6</sup> Thus, a high-dose proton-pump inhibitor is theoretically better than an H<sub>2</sub>-receptor antagonist as a treatment to prevent recurrent bleeding.

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A number of studies have evaluated the effect of proton-pump inhibitors on the risk of recurrent bleeding in patients with bleeding peptic ulcers.<sup>7-13</sup> Some of the studies did not use endoscopic treatment.<sup>7,8</sup> In some studies the numbers of patients were inadequate or the investigators were aware of the patients' treatment assignments.<sup>9-11</sup> Two recent Scandinavian trials lacked discrete outcome variables.<sup>12,13</sup> Therefore, we conducted a randomized, double-blind, placebo-controlled study to assess whether the adjuvant use of a high-dose proton-pump inhibitor after endoscopic treatment of bleeding peptic ulcers would reduce the rate of recurrent bleeding.

## METHODS

### Study Design

The study protocol was approved by the ethics committee of the faculty of medicine of the Chinese University of Hong Kong, and all patients or their next of kin provided written informed consent. From May 1998 to July 1999, all patients who were admitted to the Prince of Wales Hospital with upper gastrointestinal bleeding were treated jointly by a team of physicians and surgeons. Patients underwent endoscopy within 24 hours after admission. Those who were in shock or who were vomiting fresh blood underwent urgent endoscopy after their condition was stabilized.

At endoscopy, gastroduodenal ulcers with spurting hemorrhage, oozing hemorrhage, or nonbleeding visible vessels (defined as protruberant discolorations) were injected with epinephrine (dilution, 1:10,000). Coaptive thermocoagulation was then applied to vessels with a 3.2-mm heater probe (model CD-10Z, Olympus, Tokyo, Japan). Hemostasis was considered to have been established if bleeding had stopped and formerly bleeding vessels were flattened or cavitated. Clots covering ulcer craters were elevated by means of a heater probe or "cheese-wiring" with a mini-snare, and underlying vessels were treated. Antral-biopsy specimens were obtained and subjected to a rapid urease test (CLO test, Delta West, Bentley, Australia) to determine whether *Helicobacter pylori* was present.

Patients who were older than 16 years and in whom endoscopic treatment of actively bleeding ulcers or ulcers with nonbleeding visible vessels had been successful were eligible for the study. Patients in whom endoscopic treatment was unsuccessful were not enrolled and instead underwent immediate surgery.

### Treatment

After endoscopic treatment, patients were randomly assigned to receive an intravenous infusion of placebo or omeprazole (Losec, Astra, Mölndal, Sweden), given as an 80-mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 hours. Identical-appearing vials of omeprazole and placebo were prepared by the pharmacy department under aseptic conditions according to the international Good-Manufacturing-Practices Guidelines for Pharmaceuticals. These vials were sealed in packages according to a computer-generated list of random numbers in blocks of 80. Consecutively numbered sealed packages were delivered to the endoscopy center. When a patient fulfilled the entry criteria, a nurse at the endoscopy center opened the lowest-numbered treatment package. Treatment was started in the recovery area of the endoscopy suite and continued in a surgical ward. All vials were returned to our research office at the end of the infusion period to assess whether the drug had been delivered correctly and completely. All investigators remained unaware of the patients' treatment assignments until the study was completed.

### Follow-up

Patients were monitored in a surgical ward for signs of further bleeding. Blood pressure and pulse rate were recorded hourly during the first 24 hours of the omeprazole or placebo infusion and

every 4 hours thereafter until the patients were discharged. Bleeding was considered to have recurred if any of the following occurred: vomiting of fresh blood, shock (defined as a systolic blood pressure of 90 mm Hg or less or a pulse rate of 110 beats per minute or more) with melena after stabilization, or a drop in hemoglobin of more than 2 g per deciliter within 24 hours after a transfusion to a level of 10 g per deciliter. Patients who were judged to have recurrent bleeding underwent urgent endoscopy. Recurrent bleeding was confirmed if the ulcer was actively bleeding (spurting or oozing hemorrhage) or if there was either coffee-ground material or fresh blood in the stomach near a vessel. Endoscopic treatment with the epinephrine injection and thermocoagulation was then repeated. Surgical intervention was deemed warranted if the bleeding could not be controlled endoscopically or if there was a second recurrence of bleeding.

At the end of the omeprazole or placebo infusion, all patients were given 20 mg of omeprazole orally per day for eight weeks. Patients who had a positive rapid urease test received a one-week course of 20 mg of omeprazole twice daily, 500 mg of clarithromycin (Klacid, Abbott, Kent, United Kingdom) twice daily, and 1 g of amoxicillin (Amoxil, Bristol-Myers Squibb, Sermoneta, Italy) twice daily. These patients then received the standard dose of 20 mg of omeprazole per day for the remaining seven weeks. All patients were reevaluated at eight weeks in the outpatient clinic.

The rate of recurrent bleeding after endoscopic treatment of bleeding peptic ulcers was estimated to be 15 percent. We estimated that a minimum of 141 patients were required in each group to detect an absolute reduction of 10 percent (from 15 percent to 5 percent) in the rate of recurrent bleeding at a two-sided alpha level of 0.05 and a beta level of 0.8. We intended to recruit 320 patients and to conduct four interim analyses. The trial was terminated after the third planned interim analysis, after 240 patients had been enrolled, because we found a significant difference ( $P < 0.001$ ) between the groups in the rate of recurrent bleeding within 30 days after endoscopy (the Peto-Haybrittle rule).<sup>14</sup>

### Statistical Analysis

The Kaplan-Meier method was used to analyze the primary end point of recurrent bleeding within 30 days after endoscopy.<sup>15</sup> End-point data were analyzed according to the intention-to-treat principle. A Cox proportional-hazards model was used to adjust for possibly confounding covariates such as the presence or absence of coexisting illness, the size of the ulcer, the location of the ulcer (stomach, duodenum, or stoma), the presence or absence of a history of ulcer disease, and the American Society of Anesthesiology grade, which indicates the surgical risk.<sup>16</sup> Patients' baseline characteristics and outcome measures were compared with use of Student's *t*-test for parametric data, the Mann-Whitney *U* test for nonparametric data, and Pearson's chi-square test or Fisher's exact test for proportions.<sup>17</sup> We calculated the relative risks and 95 percent confidence intervals associated with proportions. All tests of significance were two-tailed.<sup>18</sup>

## RESULTS

Of 739 patients who were admitted with bleeding peptic ulcers, 267 received endoscopic treatment. Endoscopic treatment was not required in 472 patients who had ulcers with clean bases or flat pigments. Endoscopic treatment was unsuccessful in five patients who had profuse bleeding, and they underwent immediate surgery. Twenty-two other patients were not included in the trial: 10 had terminal cancer, 9 were moribund as a result of concomitant illnesses, and 3 did not provide consent.

A total of 120 patients were randomly assigned to receive the omeprazole infusion, and 120 to receive placebo. The study groups were similar with respect

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE 240 PATIENTS.\*

CHARACTERISTIC	OMEPRAZOLE GROUP (N=120)	PLACEBO GROUP (N=120)
Male sex — no. (%)	80 (66.7)	80 (66.7)
Age — yr	64±17.2	67±15.9
Hemoglobin — g/dl	9.4±2.7	9.5±2.6
Shock at presentation — no. of patients†	16	14
Location of ulcer — no. of patients		
Stomach	53	48
Duodenum	65	65
Stoma	2	7
Endoscopic signs of bleeding — no. of patients		
Spurting hemorrhage	14	9
Oozing hemorrhage	50	49
Nonbleeding visible vessel	38	36
Clot with underlying vessel	18	26
High-risk ulcer — no. of patients		
Posterior duodenal ulcer	17	15
Lesser-curvature gastric ulcer	12	5
Angular incisura ulcer	11	11
Size of ulcer — cm	1.2±1.1	1.1±0.8
Size of ulcer ≥2 cm — no. of patients	21	25
Previous ulcer disease — no. of patients	38	45
Previous ulcer bleeding — no. of patients	36	36
Recent use of histamine H <sub>2</sub> -receptor antagonists or proton-pump inhibitors — no. of patients	2	2
Risk factors for bleeding peptic ulcer — no. of patients		
<i>Helicobacter pylori</i> infection	78	64
Use of nonsteroidal antiinflammatory drugs	39	40
Use of aspirin	23	18
Use of warfarin	5	5
American Society of Anesthesiology grade — no. of patients‡		
I or II	70	65
III	32	35
IV	18	20
Development of bleeding during hospitalization — no. of patients§	22	23
Coexisting illnesses — no. of patients	30	40
Cerebrovascular disease	8	13
Chronic renal failure	8	4
Cardiovascular disease	3	9
Cancer	11	14
Endoscopic treatment		
Dose of epinephrine — ml	11±4	11.8±5
No. of probe pulses		
Median	8	7
Range	3–21	2–41

\*Plus-minus values are means ±SD.

†Shock was defined as a systolic blood pressure of 90 mm Hg or less or a pulse rate of 110 beats per minute or more.

‡The American Society of Anesthesiology grading system indicates the surgical risk, with higher grades indicating higher surgical risk.

§These patients had been hospitalized for other medical reasons when active bleeding of peptic ulcers began.

to demographic characteristics, the prevalence and types of coexisting illnesses, the severity of bleeding at presentation, risk factors for ulcers, the location and size of ulcers, and signs of bleeding (Table 1). All but one patient, who was in the placebo group, completed the assigned infusion according to protocol. This patient withdrew from the trial on the first

day of the infusion. No side effect related to the infusion was reported in either group.

Bleeding recurred within 30 days after treatment in 8 patients (6.7 percent) in the omeprazole group, as compared with 27 (22.5 percent) in the placebo group (hazard ratio, 3.9; 95 percent confidence interval, 1.7 to 9.0). After adjustment for the covari-

TABLE 2. OUTCOMES AFTER ENDOSCOPIC THERAPY.

OUTCOME	OMEPRAZOLE GROUP (N=120)	PLACEBO GROUP (N=120)	RELATIVE RISK (95% CI)*	P VALUE
Recurrent bleeding — no. of patients				
By day 3	5	24	4.80 (1.89–12.2)	<0.001
By day 7	7	26	3.71 (1.68–8.23)	<0.001
By day 30	8†	27†	3.38 (1.60–7.13)	<0.001
Recurrent bleeding within 30 days — no. of patients/total no.				
Actively bleeding ulcers	3/64	10/58	4.24 (1.10–16.3)	0.04
Ulcers with nonbleeding visible vessels	5/56	17/62	3.85 (1.31–11.3)	0.02
Endoscopic retreatment successful — no. of patients	6	23	3.83 (1.62–9.08)	<0.001
Surgery — no. of patients	3	9	3.00 (0.83–10.8)	0.14
Median hospital stay <5 days — no. of patients (%)	56 (46.7)	38 (31.7)		0.02
Duration of hospitalization — days				
Patients admitted for bleeding peptic ulcers				
Median	4	5		0.006
Range	3–65	3–64		
Patients in whom bleeding developed in the hospital				
Median	13	9		0.33
Range	3–40	4–46		
Units of blood transfused‡				
Before endoscopic therapy	2.7±2.5	3.5±3.8		0.04
After endoscopic therapy	1.0±1.3	1.1±1.5		0.46
After endoscopic therapy	1.7±1.9	2.4±3.2		0.03
Death within 30 days — no. of patients	5	12	2.40 (0.87–6.60)	0.13
Ulcer healing at 8 wk — no. of patients/total no. assessed endoscopically	72/85	77/83	1.10 (0.98–1.22)	0.14

\*Values indicate the relative risk of an outcome in the placebo group as compared with the omeprazole group. CI denotes confidence interval.

†This number is the total number of patients in the group who had recurrent bleeding within 30 days after treatment.

‡Plus–minus values are means ±SD.

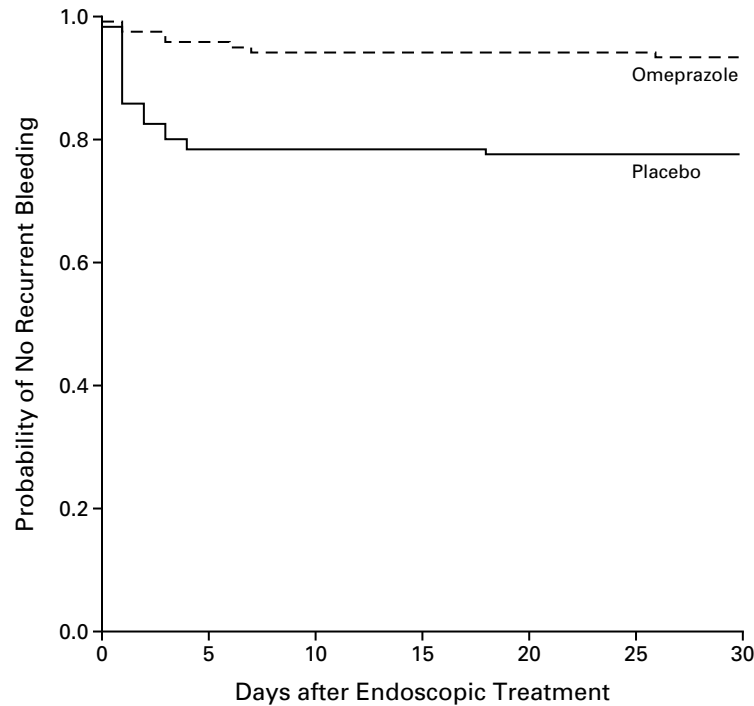
ates of the size and location of ulcers, the presence or absence of coexisting illnesses and a history of ulcer disease, and the American Society of Anesthesiology grade in the Cox proportional-hazards model, the hazard ratio was 3.9 (95 percent confidence interval, 1.7 to 9.1). Recurrent bleeding was most common during the period of infusion (i.e., within the first three days), occurring in 5 patients (4.2 percent) in the omeprazole group and 24 (20 percent) in the placebo group (relative risk, 4.80; 95 percent confidence interval, 1.89 to 12.2;  $P < 0.001$ ) (Table 2). By day 7, 7 patients in the omeprazole group (5.8 percent) had recurrent bleeding, as compared with 26 (21.7 percent) in the placebo group (relative risk, 3.71; 95 percent confidence interval, 1.68 to 8.23;  $P < 0.001$ ). At day 7, the probability that bleeding would not recur was 94.2 percent in the omeprazole group and 78.3 percent in the placebo group (Fig. 1).

When we analyzed the rate of recurrent bleeding according to the endoscopic signs of bleeding at presentation, the rate was significantly different between groups for actively bleeding ulcers and ulcers with nonbleeding visible vessels. Recurrent bleeding in the 30 days after endoscopic therapy was less common in the omeprazole group than in the placebo group among patients who had actively bleeding ulcers at

presentation (3 vs. 10 patients,  $P = 0.04$ ) or ulcers with nonbleeding visible vessels (5 vs. 17 patients,  $P = 0.02$ ).

The mean ( $\pm$ SD) number of units of blood transfused in the 30 days after endoscopy was significantly smaller in the omeprazole group than in the placebo group ( $2.7 \pm 2.5$  vs.  $3.5 \pm 3.8$  units,  $P = 0.04$ ). The difference was probably related to treatment, since the mean number of units transfused before endoscopic treatment was similar in the two groups ( $1.0 \pm 1.3$  and  $1.1 \pm 1.5$  units, respectively;  $P = 0.46$ ). The number of units transfused after endoscopic treatment was significantly smaller in the omeprazole group than in the placebo group ( $1.7 \pm 1.9$  vs.  $2.4 \pm 3.2$  units,  $P = 0.03$ ).

The duration of hospitalization was significantly shorter among patients in the omeprazole group than among those in the placebo group. The hospital stay was less than five days for 56 patients (46.7 percent) in the omeprazole group, as compared with 38 patients (31.7 percent) in the placebo group ( $P = 0.02$ ). Among the 195 patients who were initially admitted for bleeding peptic ulcers, the median stay for the 98 patients in the omeprazole group was 4 days (range, 3 to 65), as compared with a median stay of 5 days (range, 3 to 64) for the 97 patients in



NO. AT RISK							
Omeprazole	120	115	113	113	113	113	112
Placebo	120	94	93	93	93	93	93

**Figure 1.** Kaplan–Meier Estimates of the Likelihood That Bleeding Would Not Recur within 30 Days after Endoscopic Treatment.

the placebo group ( $P=0.006$ ). In the subgroup of patients in whom bleeding developed in the hospital, there was no significant difference between the groups in the median hospital stays (13 days in the omeprazole group and 9 days in the placebo group,  $P=0.33$ ).

Patients who were considered to have recurrent bleeding underwent a second endoscopy. In 6 of the 8 such patients in the omeprazole group and in 23 of 27 in the placebo group, endoscopic retreatment stopped the bleeding. The other two patients in the omeprazole group and four patients in the placebo group had profuse bleeding and underwent immediate surgery rather than endoscopic treatment. Of those in whom retreatment was initially successful, 1 of 6 in the omeprazole group and 4 of the 23 in the placebo group subsequently had a second recurrence of bleeding and underwent surgery. One additional patient in the placebo group underwent surgery because of peritonitis, due to perforation related to the heater probe, after retreatment. There were fewer surgical interventions in the omeprazole group (three vs. nine) but the difference was not significant ( $P=0.14$ ). In total, two patients, both in the placebo group, had perforations related to the heater probe.

Five patients (4.2 percent) in the omeprazole group died within 30 days after endoscopy, as compared with 12 (10 percent) in the placebo group ( $P=0.13$ ). None of the five deaths in the omeprazole group was caused by recurrent bleeding. In the placebo group, four patients died after surgery: three from duodenal-stump dehiscence after a Billroth II gastrectomy for recurrent bleeding and one patient, who had chronic renal failure, after the excision of a perforated gastric ulcer, which was probably related to thermocoagulation. Two other patients in the placebo group died from recurrent bleeding; one of these patients had active pulmonary tuberculosis and respiratory failure and was considered unfit for surgery, and the other, a 92-year-old man, died after declining surgery. The causes of death in the remaining six patients were related to their concurrent illnesses: chest infection in three, ischemic stroke in two, and liver failure in one patient with a primary liver tumor.

At eight weeks, follow-up was complete for all but two patients in the omeprazole group and four in the placebo group. In three patients (two in the omeprazole group and one in the placebo group), biopsies of the ulcers showed cancer, and they subsequently underwent surgery. Eighty-five patients in the omeprazole

razole group and 83 in the placebo group underwent follow-up endoscopy at eight weeks. The ulcers had healed in 84.7 percent (72 patients) and 92.8 percent (77 patients), respectively ( $P=0.14$ ). Among those who did not undergo follow-up endoscopy, no further bleeding was documented.

### DISCUSSION

The use of proton-pump inhibitors in patients with bleeding peptic ulcers has been evaluated in several trials. In a large, multicenter, placebo-controlled study, Daneshmend and colleagues found that the use of intravenous bolus injections of omeprazole before endoscopy had no effect on the outcome of upper gastrointestinal bleeding.<sup>7</sup> Endoscopic signs of bleeding, however, were less frequent among patients given omeprazole, suggesting that omeprazole might hasten the resolution of endoscopic signs of bleeding. Because the proportions of ulcers with specific signs of hemorrhage were not reported, ulcers with minor signs may have been included. The guidelines for endoscopic therapy were not defined. Moreover, the dose of omeprazole was insufficient to neutralize gastric pH.

In another study of 220 patients who did not undergo endoscopic treatment,<sup>8</sup> patients whose ulcers had a nonbleeding visible vessel or a clot were significantly less likely to have further bleeding when given an oral dose of 40 mg of omeprazole twice daily for five days. Two multicenter trials from Scandinavia evaluated the use of an infusion of a high dose of omeprazole in conjunction with endoscopic treatment.<sup>12,13</sup> Both reported clinical benefits with omeprazole.

Villanueva et al. treated 86 patients who had actively bleeding ulcers with an epinephrine injection and then randomly assigned them to receive intravenous ranitidine or omeprazole.<sup>9</sup> The rate of recurrent bleeding was similar in the two groups. Lin et al. used thermocoagulation to treat 100 patients whose ulcers were actively bleeding or contained a nonbleeding visible vessel and then randomly assigned them to receive an infusion of either omeprazole or cimetidine.<sup>11</sup> Patients who received omeprazole had a significantly lower rate of recurrent bleeding than those who received cimetidine. In both the study by Villanueva et al. and the study by Lin et al., the investigators were aware of the treatment assignments.

In our study, we enrolled only patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels or clots that had underlying vessels; these types of ulcer are associated with high risks of recurrent bleeding.<sup>19</sup> Complete endoscopic treatment was carried out. Ulcers with flat pigments or clean bases are at low risk for recurrent bleeding. The inclusion of patients with such ulcers would have diluted the strength of any potential association of adjuvant omeprazole therapy with clinical benefit.

During endoscopy, we used the combination of

an epinephrine injection and thermocoagulation with a 3.2-mm heater probe.<sup>20</sup> The epinephrine stops bleeding, allowing a clear view of the vessel and increasing the likelihood that the thermal device will provide firm tamponade in the appropriate place. In a canine model, thermocoagulation consistently sealed bleeding arteries that were up to 2 mm in size.<sup>21</sup> Arteries of this size are often serosal arteries stemming from larger chronic ulcers.<sup>22</sup>

We used endoscopy to confirm episodes of recurrent bleeding, and endoscopic treatment was repeated in patients with recurrence. Endoscopic retreatment can be effective in a high proportion of patients and can reduce their need for surgery.<sup>23</sup>

We did not measure intragastric pH in our patients. Studies in white subjects have demonstrated that a high dose of omeprazole, like the one we used, can neutralize intragastric pH.<sup>4-6</sup> The parietal-cell mass in Asian subjects is smaller than that in white subjects.<sup>24</sup> We therefore did not consider pH monitoring necessary. Most episodes of recurrent bleeding occurred in the first 72 hours after endoscopy in both groups — the period of infusion. The incidence of bleeding after 72 hours was low and similar in the two groups.

In conclusion, we found that after endoscopic treatment of bleeding peptic ulcers, a high-dose infusion of omeprazole reduced the rate of recurrent bleeding, decreased the need for endoscopic retreatment and blood transfusions, and shortened the length of hospitalization.

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### IMAGES IN CLINICAL MEDICINE

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The *Journal* has a large backlog of Images in Clinical Medicine that have been accepted for publication. Therefore, we will not consider new submissions in 2000. This decision will be reevaluated in December.

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