

The Effect of Endoscopic Therapy in Patients Receiving Omeprazole for Bleeding Ulcers with Nonbleeding Visible Vessels or Adherent Clots

A Randomized Comparison

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Background: The optimal treatment of ulcers with nonbleeding visible vessels and adherent clots is unclear.

Objective: To compare intravenous omeprazole infusion plus endoscopic therapy with intravenous omeprazole infusion alone for prevention of recurrent bleeding from ulcers with nonbleeding visible vessels or adherent clots.

Design: Single-blind randomized study with blinded evaluation of study end points.

Setting: An endoscopy center in a university hospital in Hong Kong.

Patients: 156 persons with upper gastrointestinal bleeding and ulcers showing nonbleeding visible vessels or adherent clots.

Intervention: Combination of endoscopic therapy and omeprazole infusion versus sham endoscopic therapy and omeprazole infusion.

Measurements: Recurrent ulcer bleeding before discharge and within 30 days.

Results: 78 patients were recruited in each group. Ulcer bleeding

recurred before discharge in seven patients who received intravenous omeprazole alone (9%) and no patients who received combined therapy (difference, 9 percentage points [95% CI, 1.7 to 17.6 percentage points]; $P = 0.01$). The probability of recurrent bleeding within 30 days was 11.6% (9 patients) in the omeprazole-alone group and 1.1% (1 patient) in the combined therapy group (difference, 10.5 percentage points [CI, 1.7 to 19.8 percentage points]; $P = 0.009$). Patients in the combined therapy group required less transfusion (difference in median units of blood transfused, 1 unit [CI, 0 to 2 units]; $P = 0.02$). One patient in the combined therapy group had surgery for ulcer perforation. Four patients receiving omeprazole alone (5.1%) and two patients receiving combined therapy (2.6%) died within 30 days.

Conclusion: The combination of endoscopic therapy and omeprazole infusion is superior to omeprazole infusion alone for preventing recurrent bleeding from ulcers with nonbleeding visible vessels and adherent clots.

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Endoscopic hemostasis is effective in controlling bleeding from peptic ulcers. The optimal treatment of ulcers with nonbleeding visible vessels and adherent clots, however, is unclear. The controversy arises from variability in endoscopic diagnosis as well as in the standard treatment strategies adopted by endoscopists for ulcers with adherent clots. At least two studies have shown that even experienced endoscopists have different definitions of stigmata at the ulcer base (1, 2). Among the stigmata of hemorrhage, clot and protuberant vessels are the most difficult to differentiate.

After a clot has been diagnosed, approaches to management are quite different. Some clinicians flush the clot with a syringe or oral irrigator, which in general produces rather weak irrigate (3), whereas others advocate targeted irrigation using thermal probes (4). With these methods of irrigation, the success rates for exposing the underlying stigmata range from 9% (3) to 57% (4). Even after removal of blood clots, it is not certain whether endoscopic therapy prevents recurrent bleeding or actually provokes it. Randomized, controlled trials of endoscopic therapy versus no endoscopic therapy have yielded conflicting results (5, 6), and meta-analysis does not support routine use of endoscopic therapy (7).

The advent of proton-pump inhibitors changed the

standard of practice in the management of bleeding ulcers. Two studies from India have demonstrated the benefit of high-dose oral omeprazole for peptic ulcer bleeding. Khuroo and colleagues (8) demonstrated that a 5-day course of oral omeprazole, 40 mg twice daily, reduced recurrent bleeding even without endoscopic therapy. The benefit of omeprazole was most remarkable among patients with visible vessels or adherent clots at the ulcer bases. Javid and associates (9) showed that the same omeprazole regimen in combination with endoscopic injection prevented recurrent bleeding. Their study, however, failed to demonstrate a distinct advantage of omeprazole in patients with nonbleeding visible vessels and adherent clots.

A recent randomized study by Jensen and coworkers (10) compared twice-daily administration of an oral proton-pump inhibitor with endoscopic therapy in 32 patients who were at high risk for ulcer hemorrhage. Six of 17 medically treated patients had recurrent bleeding compared with none of 15 patients treated endoscopically. The study was discontinued prematurely because of the dramatic difference in clinical outcome. Study limitations included small sample size, unequal distribution of confounding factors, and lack of difference in clinical end points (11).

The effectiveness of proton-pump inhibitors alone for ulcers that are not actively bleeding but have stigmata of a

Context

Endoscopic hemostasis plus omeprazole in patients with actively bleeding ulcers prevents recurrent bleeding. Are both needed if endoscopy shows a nonbleeding vessel or nonbleeding clot?

Contribution

This randomized trial included 156 patients admitted for bleeding whose endoscopies, performed within 24 hours of admission, showed ulcers with nonbleeding vessels or adherent clots. Approximately 12% of patients receiving omeprazole alone had recurrent bleeding within 30 days compared with approximately 1% who received endoscopic hemostasis (thermocoagulation and epinephrine injection) plus omeprazole.

Implications

Endoscopic hemostasis plus omeprazole better prevents recurrent bleeding than does omeprazole alone in patients who have recently bled from an ulcer but do not have actively bleeding vessels at endoscopy.

—The Editors

nonbleeding visible vessel or an adherent clot remains undetermined. We previously demonstrated that high-dose intravenous omeprazole as an adjunct to endoscopic therapy substantially reduced risk for recurrent bleeding, repeated endoscopy, frequency of blood transfusion, and duration of hospitalization (12). Subgroup analysis suggested that actively bleeding ulcers, as well as ulcers with a nonbleeding visible vessel or an adherent clot, benefited from the treatment. In the current study, we compared high-dose intravenous omeprazole infusion plus endoscopic therapy with intravenous omeprazole infusion alone for prevention of recurrent bleeding from ulcers with a nonbleeding visible vessel or an adherent clot.

METHODS**Description of the Study and Patients**

We performed a single-center randomized trial comparing the combination of endoscopic therapy and high-dose omeprazole infusion with high-dose omeprazole infusion alone for treatment of ulcers with a nonbleeding visible vessel or an adherent clot. This study was conducted at the Endoscopy Center of the Prince of Wales Hospital in Hong Kong. The clinical trials ethics committee of the faculty of medicine of the Chinese University of Hong Kong approved the study protocol.

Consecutive patients who presented with signs of upper gastrointestinal bleeding underwent endoscopic examination within 24 hours of hospital admission. Patients who were in shock or were vomiting fresh blood at presentation underwent urgent endoscopy as soon as their hemodynamic conditions stabilized. All endoscopic examina-

tions were performed by using a dual-channel endoscope (Olympus 2T200, Olympus Japan Co., Tokyo, Japan). All participants provided written informed consent before the endoscopic examinations. At endoscopy, gastric or duodenal ulcers were examined to determine whether they were actively bleeding (spurting or oozing) or showed nonbleeding visible vessels or adherent clots. A nonbleeding visible vessel was defined as “a protuberant discoloration” according to the National Institutes of Health 1989 consensus statement (13). Ulcers with overlying clots were irrigated for 5 minutes with a 3.2-mm heater probe (Olympus CD-10Z, Olympus Japan Co.) to remove loosely attached clots and debris. An adherent clot was defined as a blood clot that remained attached to the ulcer base after the 5-minute period of irrigation (3).

Patients met the inclusion criteria if they were at least 16 years of age and had benign gastroduodenal ulcers showing nonbleeding visible vessels or adherent clots at endoscopy. Patients were excluded if they 1) had actively bleeding ulcers, including ulcers in which endoscopic irrigation procedures provoked bleeding before treatment; 2) had had endoscopic therapy for bleeding ulcer within the past 30 days; 3) had a history of gastric surgery; 4) were pregnant; 5) had malignant ulcers; or 6) did not provide written informed consent. Specimens were taken from the antrum for urease biopsy and histologic examination to determine *Helicobacter pylori* status. Patients found to have malignant ulcers after initial enrollment were excluded from the analysis.

Randomization and Treatment Protocol

Randomization was performed when ulcers were judged to show a nonbleeding visible vessel or an adherent clot after 5 minutes of irrigation. Patients were randomly assigned to receive endoscopic therapy or sham endoscopic treatment. Randomization was carried out through the use of a computer-generated list of random numbers in blocks of 10. Allocation concealment was performed by an independent research nurse who assigned treatments according to consecutive numbers in sealed opaque envelopes. Patients randomly assigned to endoscopic therapy were treated with epinephrine injection followed by thermocoagulation. Diluted epinephrine (1:10 000 dilution) was injected in 0.5-mL or 1-mL aliquots around the nonbleeding visible vessels or adherent clots to induce tissue blanching and edema. In general, approximately 5 mL of diluted epinephrine was injected. The vessels were then thermocoagulated by using a 3.2-mm heater probe (30 J for 6 seconds). The end point of endoscopic treatment was defined by the flattening or “cavitation” of protuberances. Adherent clots were removed by cheese-wiring using a mini-snare, and the ulcer base was again examined. Underlying vessels were coagulated in a similar fashion. In the event of provoked bleeding, cessation of bleeding and flattening or “cavitation” of protuberances constituted successful treatment. Patients randomly assigned to sham endoscopic treatment

underwent gentle irrigation of the ulcer base using a syringe but no manipulation with the heater probe, mini-snare, or suction. Any bleeding provoked after randomization was included in the intention-to-treat analysis.

All patients received intravenous omeprazole (Losec, AstraZeneca, Molndal, Sweden) after randomization. A bolus injection of omeprazole, 80 mg, was given during the endoscopic procedure and was followed immediately by a continuous infusion of 8 mg/h for 72 hours.

Follow-up

After the endoscopic procedure, an independent team of physicians who were blinded to treatment assignments monitored the patients in a gastroenterology ward for signs of recurrent bleeding. The endoscopists were not involved in subsequent patient management. A research nurse kept endoscopy records in opaque sealed envelopes that were not accessible to physicians, investigators, or patients. Blood pressure and pulse rate were monitored hourly during the first 24 hours and every 4 hours thereafter until discharge.

After finishing 72 hours of omeprazole infusion, patients were prescribed 20 mg of oral omeprazole per day. Those who had no evidence of recurrent bleeding were discharged within 5 days of hospitalization. Patients who had positive results on urease biopsy also received a 1-week course of omeprazole (20 mg twice daily), clarithromycin (500 mg twice daily), and amoxicillin (1 g twice daily). All patients were evaluated for evidence of delayed recurrent bleeding at day 30.

End Points

The primary end points were recurrent ulcer bleeding before discharge and within 30 days, according to prespecified criteria. Bleeding was considered to have recurred if any of the following were documented: vomiting of fresh blood; shock (defined as a systolic blood pressure < 90 mm Hg or pulse rate > 110 beats/min) with melena after stabilization; or a decrease in hemoglobin level of more than 20 g/L within 24 hours after transfusion, to a level of 100 g/L. The need for subsequent transfusion was left to the discretion of the attending physicians, who were blinded to allocated treatment. Patients in whom recurrent bleeding was suspected underwent urgent endoscopy. Surgical intervention was deemed warranted if the bleeding could not be controlled by endoscopy or if complications arose from endoscopic therapy. Only events adjudicated by a team of independent blinded physicians according to these prespecified criteria were included in the outcome analysis. Secondary end points included blood transfusion requirement, duration of hospital stay, surgery requirement, and death within 30 days after index bleeding.

Statistical Analysis

We planned the sample size on the basis of the assumption that 7% of patients receiving combined therapy and 25% of patients receiving omeprazole infusion alone would develop recurrent ulcer bleeding in 30 days (12).

We estimated that with an overall sample size of 156 patients, 5% of whom would drop out, a two-sided log-rank test would achieve a power of 80% at a 5% significance level (PASS software, version 2000, NCSS Statistical Software, Kaysville, Utah).

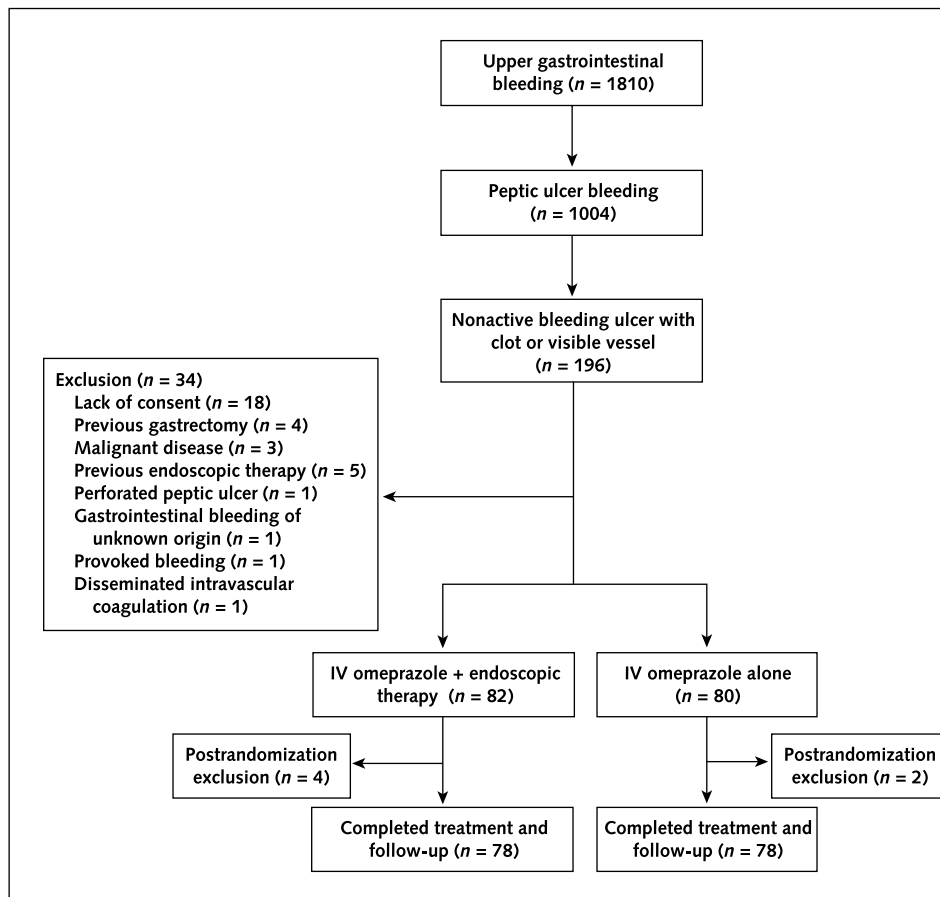
Homogeneity of the treatment groups at baseline was analyzed by using the Pearson chi-square test or the Fisher exact test (StatXact 4 for Windows, version 4.0, Cytel Software Corp., Cambridge, Massachusetts) for categorical data and the Student *t*-test for continuous variables. End point data were analyzed on the basis of the intention-to-treat population, which was defined as all randomly assigned patients except those who had malignant ulcers. Patients who withdrew from treatment early were followed until the end of the study to determine whether bleeding had recurred. We used the Fisher exact test to compare the proportions of patients who had recurrent ulcer bleeding before discharge. The Kaplan–Meier method was used to estimate the likelihood of recurrent ulcer bleeding within 30 days. Duration of hospital stay and transfusion requirement were analyzed by using the Mann–Whitney *U* test. An exact logistic regression model (LogXact 4 for Windows, version 4.1, Cytel Software Corp.) was used to adjust for potential baseline imbalance in important prognostic variables, including the size of ulcers (<2 cm or ≥2 cm), the location of ulcers (gastric or duodenal), the development of ulcer bleeding after hospitalization, and the presence or absence of nonbleeding visible vessels. All *P* values and 95% CIs are two-sided.

RESULTS

In the 18-month period from January 2001 to July 2002, 1810 patients were admitted to the Prince of Wales Hospital with upper gastrointestinal bleeding. Among them, 1004 were found to have peptic ulcers. One hundred seventy-eight patients had active ulcer bleeding (spurting or oozing), and 196 patients had nonactive bleeding ulcer with visible vessel or clot. Of these 196 patients, 162 were recruited for the study and 34 were excluded. Among the latter group, 18 did not provide consent, 4 had had previous gastrectomy, 3 had terminal malignant disease, 5 had had previous endoscopic therapy within 30 days, 1 had a perforated ulcer, 1 with a clot had bleeding provoked by endoscopic manipulation before randomization, 1 had gastrointestinal bleeding of unknown origin, and 1 had disseminated intravascular coagulation. Six patients in whom malignant ulcers were subsequently confirmed were excluded after randomization (Figure 1).

Seventy-eight patients were randomly assigned to receive intravenous omeprazole plus endoscopic therapy (combined therapy group), and 78 were randomly assigned to receive intravenous omeprazole plus sham endoscopic therapy (omeprazole-alone group). The two groups were similar in demographic characteristics, such as symptoms at presentation, clinical status at admission (blood pressure,

Figure 1. Trial profile.



IV = intravenous.

hemoglobin levels), characteristics of ulcers (location, size, and stigmata of bleeding), history of peptic ulcer bleeding and risk factors, prevalence and types of coexisting illness, and American Society of Anesthesiology grade (Table 1).

Twelve patients with suspected recurrent bleeding underwent endoscopy a second time and were evaluated by the adjudication committee. The committee identified 10 cases of recurrent bleeding according to prespecified criteria. Two patients in the combined therapy group did not meet the prespecified criteria because they had a decrease in hemoglobin level but no clinical or endoscopic evidence of recurrent bleeding. Recurrent ulcer bleeding during the first 72 hours was documented in three patients who received intravenous omeprazole alone but in none of those who received combined therapy ($P > 0.2$ [Fisher exact test]). During hospitalization, seven patients who received intravenous omeprazole alone (9%) and no patients who received combined therapy developed recurrent bleeding (difference, 9 percentage points [95% CI, 1.7 to 17.6 percentage points]; $P = 0.01$ [Fisher exact test]). Among these seven patients, four had recurrent bleeding after discontinuation of intravenous omeprazole. Two additional patients in the omeprazole-alone group and one in the combined therapy group bled again after discharge from the hospital.

Taken together, nine patients in the omeprazole-alone group and one in the combined therapy group had recurrent ulcer bleeding within 30 days after the index bleeding episode. None of the patients who developed recurrent bleeding did so during the same hospital admission—that is, all recurrent bleeding developed after discharge. The probability of recurrent bleeding within 30 days was 11.6% (CI, 4.5% to 18.8%) in the omeprazole-alone group and 1.1% (CI, 0% to 3.9%) in the combined therapy group (difference, 10.5 percentage points [CI, 1.7 to 19.8 percentage points]; $P = 0.009$ [log-rank test]) (Figure 2). After we adjusted for the size and location of ulcers, inpatient bleeding, and nonbleeding visible vessels in the exact regression model, the relative risk was 11.6 (CI, 1.5 to 530.7). None of the patients took aspirin or nonsteroidal anti-inflammatory drugs during the 30-day follow-up period. All patients with recurrent bleeding in the omeprazole alone group were successfully treated with endoscopic therapy.

Among those who had nonbleeding visible blood vessels, 9 of 54 patients in the omeprazole alone group (16.7%) and none of 63 patients in the combined therapy group had recurrent bleeding ($P = 0.001$ [Fisher exact test]). Among those who had adherent clots, none of 24 patients in the omeprazole alone group and 1 of 15 pa-

Table 1. Baseline Characteristics of the Study Sample*

Characteristic	Combined Therapy Group (n = 78)	Omeprazole-Alone Group (n = 78)
Women/men, n/n	23/55	19/59
Age, y	63.1 ± 17.2	66.0 ± 16.7
Hemoglobin level, g/L	99 ± 23	95 ± 28
Lowest blood pressure at presentation, mm Hg	114.4 ± 23.2	113.7 ± 22.8
Shock at presentation, n	16	15
Symptom at presentation, n		
Hematemesis	8	8
Melena	58	58
Both hematemesis and melena	9	9
Anemia	1	3
Others	2	0
Location of ulcer, n		
Stomach	30	40
Duodenum	48	38
Endoscopic signs of bleeding, n		
Nonbleeding visible vessel	63	54
Adherent clot	15	24
High-risk ulcer, n	15	15
Posterior duodenal ulcer	5	4
Lesser-curvature gastric ulcer	3	3
Angular incisura ulcer	7	8
Size of ulcer, cm	1.2 ± 0.6	1.3 ± 1.0
Ulcer ≥ 2 cm, n	11	17
Previous ulcer disease, n	17	21
Previous ulcer bleeding, n	18	18
Risk factors for bleeding ulcer, n		
<i>Helicobacter pylori</i> infection	50	51
Use of nonsteroidal anti-inflammatory drug		
At enrollment	24	30
During 30-day follow-up	0	0
Use of aspirin		
At enrollment	21	21
During 30-day follow-up	0	0
American Society of Anesthesiology grade, n		
I/II	51	54
III	23	17
IV	4	6
V	0	1
Inpatient bleeding, n	5	12
Coexisting illness, n†		
Cerebrovascular disease	6	9
Chronic renal failure	1	4
Congestive heart failure	0	4
Myocardial infarction	9	9
Cancer	6	3
Multiple organ failure	1	5
Endoscopic treatment		
Dose of epinephrine, mL	9.1 ± 3.0	NA
Median probe pulses (range), n	6 (0–35)	NA

* Values presented with a plus/minus sign are means ± SD. NA = not applicable.
† Some patients had more than one coexisting illness.

tients in the combined therapy group (6.7%) had recurrent bleeding ($P > 0.2$ [Fisher exact test]). The median number of units of blood transfused within 30 days was significantly lower in those who received combined therapy (median, 2 units [range, 0 to 7 units]) than in those who received intravenous omeprazole alone (median, 2.5 units [range, 0 to 13 units]) (difference, 1 unit [CI, 0 to 2 units]; $P = 0.02$ [Mann–Whitney U test]). The difference was probably related to the assigned treatment, since the num-

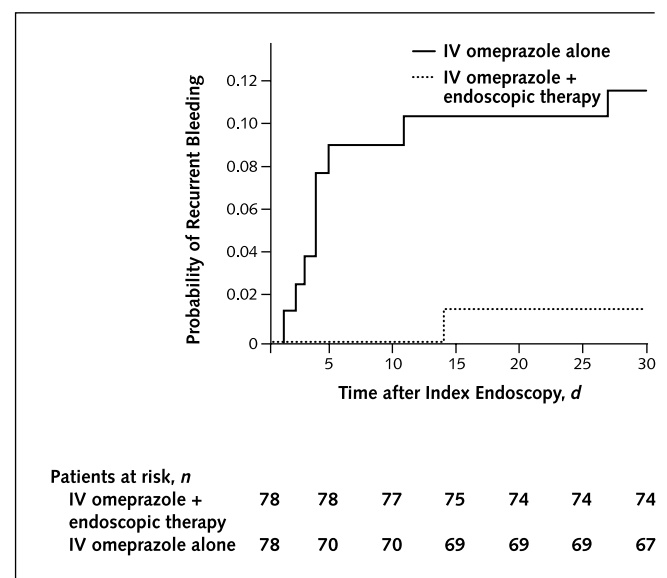
ber of units transfused before endoscopy was similar in the two groups (Table 2). Duration of hospital stay did not differ significantly between the two groups ($P = 0.06$). Fewer patients in the combined therapy group stayed in the hospital for more than 5 days, the median length of stay ($P = 0.03$).

Only one patient required surgery, a man who had a duodenal ulcer with a nonbleeding visible vessel and was assigned to the combined therapy group. The ulcer was perforated during the endoscopic procedure, and the patient died within 30 days despite successful repair. In total, four patients in the omeprazole-alone group died within 30 days after endoscopy compared with two patients in the combined therapy group (5.1% vs. 2.6%; $P > 0.2$). In the combined therapy group, in addition to the patient who died of ulcer perforation, one patient died of pneumonia and motor neuron disease. In the omeprazole-alone group, causes of death included bowel ischemia in one patient, pneumoconiosis in one patient, metastatic carcinoma of the liver in one patient, and rectosigmoid cancer in one patient.

DISCUSSION

Data from previous studies indicated that bleeding recurs in 30% to 50% of peptic ulcers with nonbleeding visible vessels and adherent clots that are not treated with endoscopy (5, 6, 14). In our previous series of 778 patients with severe ulcer bleeding, 29% of those with adherent clots and 39% of those with visible vessels developed recurrent bleeding during hospitalization (15). These data are consistent with a recent randomized trial by Jensen and coworkers (10).

Figure 2. Kaplan–Meier estimates of the likelihood of recurrent ulcer bleeding within 30 days.



IV = intravenous.

Table 2. Outcomes

Outcome	Combined Therapy Group (n = 78)	Omeprazole-Alone Group (n = 78)	P Value
Endoscopy-confirmed recurrent bleeding, n			
Within 72 h	0	3	>0.2
Before discharge	0	7	0.01
By day 30	1	9	0.009
Successful endoscopic retreatment, n	0	7	0.01
Surgery, n	1	0	>0.2
Median duration of hospitalization (range), d	5 (3–22)	5 (3–29)	0.06
Median units of blood transfused (range), n			
Before endoscopic therapy	0 (0–3)	0 (0–4)	0.07
Total blood transfusion	2 (0–7)	2.5 (0–13)	0.02
In-hospital death, n	2	3	>0.2
Death within 30 days, n	2	4	>0.2

Such a high rate of morbidity is unacceptable. Ulcers with protuberant vessels and adherent clots warrant better therapy, whether pharmacologic or endoscopic. In the study by Jensen and coworkers (10), patients received an oral proton-pump inhibitor twice daily, but the rebleeding rate remained high. The type and dosage of proton-pump inhibitor used were not specified. Khuroo and colleagues (8), in contrast, showed that recurrent bleeding rate was reduced to 11.8% among those with visible vessels who received oral omeprazole, 40 mg twice daily, for 5 days. Our present study confirms that intravenous therapy with the proton-pump inhibitor omeprazole reduces the risk for recurrent bleeding to just over 10%. The recurrent bleeding rate of 11.5% in our study, which arose predominantly from ulcers with visible vessels rather than those with adherent clots, is highly consistent with the results of Khuroo and colleagues (8). Although for ethical reasons we did not include a control group without endoscopic treatment or proton-pump inhibitors, our data indicate a substantial improvement when compared with previous rebleeding rates of 30% to 50% (5, 6, 14).

Can we do better? Our results show that when endoscopic therapy is combined with a potent acid suppressant, risk for recurrent bleeding can be further reduced to a minimal level. Only 1 of 78 patients who received combined endoscopic and pharmacologic therapy developed recurrent bleeding within 30 days of follow-up. These data suggest that attempts to seal underlying blood vessels at the ulcer base and stabilize blood clots work synergistically in preventing further bleeding from peptic ulcers. Patients treated with this strategy required less blood transfusion and probably had shorter hospital stays as a result of fewer episodes of recurrent bleeding. However, because we observed relatively few cases of recurrent bleeding, no significant reduction in surgery and 30-day mortality rates could be demonstrated.

We found that rates of recurrent bleeding from ulcers showing adherent clots were low in both treatment groups. Reported series in the literature often cite a higher risk for recurrent bleeding in ulcers with nonbleeding visible ves-

sels than in those with clots (14). Our data suggest that high-dose intravenous omeprazole alone may be useful in stabilizing adherent clots. The low incidence of recurrent bleeding associated with adherent clots could also be related to the rigorous endoscopic washing technique we used. Initial targeted irrigation with a 3.2-mm probe often unveils an underlying vessel, which we would have classified as a nonbleeding visible vessel at trial entry rather than as an adherent clot.

We should also point out that in patients treated with intravenous omeprazole alone, bleeding can recur after therapy with intravenous medication is discontinued. In our study, six of nine patients in the omeprazole-alone group bled after intravenous medication was stopped. This suggests that a higher dose of oral omeprazole should be used after completion of omeprazole infusion to prevent delayed recurrent bleeding. If it is assumed that bleeding recurs in 30% of patients who do not receive both omeprazole and endoscopic therapy, 5.4 patients needed to be treated for benefit with intravenous proton-pump inhibitor but only 3.5 needed to be treated for benefit by combination therapy to avoid one recurrent bleeding episode.

To achieve effective hemostasis, the overlying blood clot must be removed to expose the hemorrhage site at the ulcer base. Many endoscopists are reluctant to lift blood clots from ulcers because of the risk for provoking severe bleeding. Our approach, which is similar to that of Jensen and coworkers (10), is to start with targeted washing using the thermal probe. If the clot cannot be washed away, a small amount of epinephrine is injected into the ulcer base before mechanical methods are used to remove blood clot. In our study, only one patient had bleeding provoked by manipulation of the clot before randomization. The risk associated with manipulating blood clots in previous reports has also been very low (3, 4, 10). This procedure is probably more hazardous in centers where clinicians are less experienced in handling peptic ulcer bleeding. However, targeted irrigation has been shown repeatedly to be safe and should be widely adopted in managing ulcers with adherent clot. One patient in our study had a perforated

ulcer as a result of endoscopic treatment. However, this is a known complication of endoscopic therapy, especially when thermal coagulation is used, and should not be a deterrent.

The incidences of recurrent bleeding in both of our treatment groups were somewhat lower than those quoted in our sample size estimation. When calculating the required sample size, we extrapolated data from our previous trial on the adjunctive use of omeprazole infusion and endoscopic therapy, which included patients with ulcers showing active bleeding or major stigmata (12). However, no data were available in the literature on the incidence of recurrent bleeding among ulcers with major stigmata treated with omeprazole infusion alone. We assumed that the rate of recurrent bleeding was 25%, knowing that without some form of treatment, it would have been between 29% and 40% (15). The lower-than-expected failure rates could be due to the exclusion of patients with actively bleeding ulcers. Alternatively, omeprazole infusion may in fact be useful as a sole treatment. This would have been difficult to confirm unless we introduced a placebo group, which would have posed ethical complications. The relatively small sample size in our study and the small numbers of events might have overestimated the true treatment efficacy. The actual benefit of combined endoscopic and pharmacologic therapy for ulcers with major stigmata should be confirmed by large-scale studies.

Endoscopic hemostasis and proton-pump inhibitors have been proven to be efficacious therapy for actively bleeding ulcers. Our results suggest that the combination of endoscopic therapy and omeprazole infusion is superior to omeprazole infusion alone in preventing recurrent bleeding from ulcers showing adherent clots or nonbleeding visible vessels.

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