

## A COMPARISON OF OMEPRAZOLE AND PLACEBO FOR BLEEDING PEPTIC ULCER

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### ABSTRACT

**Background** The role of medical treatment for patients with bleeding peptic ulcers is uncertain.

**Methods** We conducted a double-blind, placebo-controlled trial in 220 patients with duodenal, gastric, or stomal ulcers and signs of recent bleeding, as confirmed by endoscopy. In 26 patients the ulcers showed arterial spurting, in 34 there was active oozing, in 35 there were nonbleeding, visible vessels, and in 125 there were adherent clots. The patients were randomly assigned to receive omeprazole (40 mg given orally every 12 hours for five days) or placebo. The outcome measures studied were further bleeding, surgery, and death.

**Results** Twelve of the 110 patients treated with omeprazole (10.9 percent) had continued bleeding or further bleeding, as compared with 40 of the 110 patients who received placebo (36.4 percent) ( $P < 0.001$ ). Eight patients in the omeprazole group and 26 in the placebo group required surgery to control their bleeding ( $P < 0.001$ ). Two patients in the omeprazole group and six in the placebo group died. Thirty-two patients in the omeprazole group (29.1 percent) and 78 in the placebo group (70.9 percent) received transfusions ( $P < 0.001$ ). A subgroup analysis showed that omeprazole was associated with significant reductions in recurrent bleeding and surgery in patients with nonbleeding, visible vessels or adherent clots, but not in those with arterial spurting or oozing.

**Conclusions** In patients with bleeding peptic ulcers and signs of recent bleeding, treatment with omeprazole decreases the rate of further bleeding and the need for surgery. (N Engl J Med 1997;336:1054-8.)

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**B**LEEDING in the upper gastrointestinal tract is an important cause of hospital admission and death, with an overall incidence of approximately 150 hospital admissions per 100,000 population per year.<sup>1</sup> Endoscopic techniques are widely used to treat patients with bleeding from a peptic ulcer and stigmata of recent hemorrhage.<sup>2-7</sup> Medical therapy is an attractive alternative for controlling ulcer-related hemorrhage and preventing its recurrence.<sup>8-11</sup> The function of platelets is severely impaired at low pH in vitro. Pepsin can digest blood clots overlying ulcer craters, and its activity is pH-related. Thus, a profound reduction of gastric acidity so that the pH approaches neutrality

could stabilize the clot over an ulcer and stop bleeding or prevent a recurrence.<sup>12-14</sup>

Trials of histamine H<sub>2</sub>-receptor antagonists in patients with bleeding peptic ulcers have not demonstrated a significant benefit associated with treatment.<sup>8,9</sup> A meta-analysis of 27 published trials of the use of H<sub>2</sub>-receptor antagonists in such patients suggested that the drugs marginally reduce the rate of referral for surgery and the mortality rate, notably among those with gastric ulcers.<sup>15</sup> In a large trial of more than 1000 patients with bleeding in the upper gastrointestinal tract, intravenous famotidine treatment did not affect the need for transfusion, the operative rate, or mortality.<sup>11</sup> These results, though disappointing, do not establish that gastric acidity is unimportant in the pathogenesis of further bleeding in patients with bleeding peptic ulcers. Clinical trials in such patients have frequently been either flawed in their design or too small for treatment effects to be detected.<sup>16</sup> We compared omeprazole with placebo for the treatment of bleeding peptic ulcers.

### METHODS

#### Study Design

Between January 1992 and August 1994, all patients admitted to the Sheri Kashmir Institute of Medical Sciences, Srinagar, India, with bleeding in the upper gastrointestinal tract were considered for inclusion in the study. Upper gastrointestinal bleeding was suspected only if members of the medical or nursing staff witnessed either hematemesis or melena (the passage of tarry stool); recovered bloody nasogastric aspirate; or saw black, tarry material on rectal examination. After fluid resuscitation, the patients underwent endoscopy of the upper gastrointestinal tract within 12 hours of admission. Those with duodenal, gastric, or stomal ulcers and stigmata of recent hemorrhage were enrolled in the study. Stigmata of recent hemorrhage were arterial spurting; the presence of a nonbleeding, visible vessel (appearing as a discrete red or bluish protuberance in the ulcer crater); oozing from the ulcer that on washing did not reveal a visible vessel or any of the other signs; and the presence of an adherent clot over the ulcer that could not be dislodged on gentle washing with a jet of water delivered through the channel of the endoscope.<sup>17-19</sup> Flat, pigmented spots over the ulcer were not considered stigmata of recent hemorrhage. At the time of endoscopy, we estimated the size of the ulcer by placing biopsy forceps alongside the ulcer; the fully opened cup of the forceps was 5 mm in diameter.<sup>20</sup>

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Patients were excluded from the study if they had severe terminal illness that made endoscopic examination hazardous or undesirable; profuse hemorrhage accompanied by persistent shock, during which the upper gastrointestinal tract was filled with fresh blood, limiting visibility through the endoscope and necessitating emergency surgery as a life-saving procedure; or bleeding from a Mallory-Weiss tear, varices, erosions, tumors, or an unknown source. Eligible patients were randomly assigned to receive omeprazole (Protoloc, US Vitamins, Bombay, India) or an identical-looking placebo. The randomization was carried out in the endoscopy laboratory with the use of sealed envelopes. Omeprazole was administered orally (40 mg every 12 hours) for five days. (No intravenous preparation was available.) Both study groups were allowed to receive a liquid antacid (Digene, Boots Pharmaceutical, Bombay, India; 15 ml orally every six hours). None of the patients were given H<sub>2</sub>-receptor antagonists, because such treatment has not been demonstrated to have a significant benefit with respect to acute bleeding in the upper gastrointestinal tract.<sup>8,9</sup> The study was conducted in a double-blind manner, and all the treatment assignments were revealed at the end of the study. All the patients gave written informed consent. The study was approved by the Ethical Committee and the Clinical Research Committee of the institute.

After endoscopy, we serially monitored each patient's vital signs, hemoglobin concentration (every 12 hours for five days, then daily until discharge), volume replacement, and urinary output. Endoscopy was repeated within 72 hours when there was a clinical suspicion of further bleeding or a need to define the initial findings further in patients with ulcers covered by adherent clots. Otherwise, decisions about patient care were made by the treating physicians.

#### Study Data

For each patient, data were recorded on the following: demographic variables, any prior use of nonsteroidal antiinflammatory drugs (NSAIDs), the presence or absence of IgG antibodies to *Helicobacter pylori*, preexisting medical conditions, the pattern and amount of bleeding, hemodynamic status (as measured serially), hemoglobin concentrations, endoscopic findings, and the hospital course. Preexisting medical conditions were defined as cardiovascular (a history of myocardial infarction, angina pectoris, or congestive heart failure), respiratory (pneumonia or chronic obstructive pulmonary disease with respiratory failure), or renal (known renal disease, with a serum creatinine concentration above 3.0 mg per deciliter [265 μmol per liter]).

#### Definitions

Continued bleeding was defined as persistent hemorrhage from a peptic ulcer, with spurting or oozing from an artery, on the initial endoscopic examination. Such bleeding was revealed by the presence of a bloody nasogastric aspirate, shock (a pulse greater than 100 beats per minute, a systolic blood pressure of less than 100 mm Hg, or both), and the need for substantial replacement of blood and fluid volume (the transfusion of ≥3 units of blood within four hours) and was confirmed at surgery performed within a few hours of admission. A recurrence of bleeding (further bleeding) was defined by the vomiting of fresh blood, melena, or both (with either shock or a decrease in the hemoglobin concentration by at least 2 g per deciliter over a 24-hour period) after the early stabilization of pulse, blood pressure, and the hemoglobin concentration. Endoscopy was repeated, and in some cases surgery was performed, to confirm the clinical suspicion of recurrent bleeding.

Surgery was performed when the patient had shock on presentation and there was clinical evidence of continued bleeding that required rapid volume replacement (≥3 units of blood within four hours). Recurrences of bleeding were initially managed conservatively, with surgery indicated when the patient's condition did not stabilize and the patient required 4 or more units of blood in a 24-hour period. We chose to treat patients surgically if they had continued bleeding or a recurrence of bleeding. With consid-

erable demand for endoscopic therapy in the hospital and only one physician trained to perform it, we considered that conducting this study would be impractical if endoscopic therapy were given on an emergency basis to every patient with continued bleeding or recurrent bleeding. Mortality was defined as death within 30 days after admission from causes related to bleeding or the treatment of the ulcer or any of the specified preexisting medical conditions. The data on transfusions included the number of units of blood transfused per patient during the hospital stay and the total number of patients in each study group who received transfusions.

#### Study Size

We found earlier that patients with bleeding peptic ulcers and stigmata of recent hemorrhage had recurrent bleeding at a rate of about 40 percent and surgery at a rate of about 30 percent. Therefore, we postulated that a sample of 220 subjects would give the study a power of 0.9 at a 5 percent level of significance ( $\alpha = 0.05$ ) to detect a 50 percent reduction in the rate of recurrent bleeding in the treatment group and a power of 0.8 to detect a 50 percent reduction in the rate of surgery in that group.<sup>21</sup>

#### Statistical Analysis

Student's t-test, the chi-square test for proportions, and two-tailed Fisher's exact tests were used in the analysis as appropriate.<sup>21</sup> To test the association between outcome and omeprazole therapy, we estimated risk ratios and 95 percent confidence intervals. The odds ratios were adjusted for confounding factors by logistic regression. We calculated the confidence intervals associated with proportions, the differences between proportions, and odds ratios with the methods of Fleiss, using corrections for continuity and two-tailed tests of significance.<sup>22</sup> A number of covariables were studied by logistic regression to determine their influence on outcomes. Data are presented as means ±SD.

## RESULTS

During the study period, 869 patients with bleeding in the upper gastrointestinal tract were screened for inclusion in the study. Nine had profuse bleeding, were in shock despite active resuscitative measures, and underwent immediate surgery. All nine had large ulcers of the posterior duodenum that had eroded into major vessels. The surgical procedure involved running a suture under a bleeding vessel in the ulcer bed and performing pyloroplasty. Eight patients recovered, and one died of acute renal failure.

Among the remaining 860 patients, emergency endoscopy revealed duodenal ulcers in 533 patients, gastric ulcers in 102, stomal ulcers in 45, esophageal varices in 52, gastric erosions in 43, gastric tumors in 36, Mallory-Weiss tears in 34, hemobilia in 2, gastric leiomyomas in 2, an arteriovenous malformation in 1, and normal findings in 10. Of the 680 patients with peptic ulcers, 220 (32.4 percent) had endoscopically detectable stigmata of recent hemorrhage: arterial spurting in 26 (11.8 percent); active oozing in 34 (15.5 percent); nonbleeding, visible vessels in 35 (15.9 percent); and adherent clots in 125 (56.8 percent). At the time of randomization, 110 patients were assigned to receive omeprazole, and the remaining 110 to receive placebo. The study groups were similar with respect to demographic variables, modes of presentation, severity of

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS WITH BLEEDING PEPTIC ULCERS.\*

CHARACTERISTIC	OMEPRAZOLE (N=110)	PLACEBO (N=110)
Age (yr)		
Mean	58±8	56±8
Range	40–68	40–68
Sex (no. of patients)		
Male	68	66
Female	42	44
Condition at presentation (no. of patients)		
Hematemesis	25	21
Melena	64	61
Both	21	28
Mean blood pressure (mm Hg)		
Systolic	116±4.8	115±5.0
Diastolic	84±4.3	83±5.4
Pulse (beats/min)		
Mean	98±5.5	96±4.2
Range	90–110	92–110
Hemoglobin (g/dl)		
Mean	9.8±0.6	9.6±0.8
Range	9–11	8.8–10.5
NSAID use, past 7 days (no. of patients)	17	20
Associated medical illness (no. of patients)	7	5
Cardiac	2	3
Pulmonary	5	0
Renal	0	2
Smokers (no.)†	77	75
<i>Helicobacter pylori</i> (no. positive)	78	81
Ulcer site (no. of patients)		
Duodenum	88	95
Stomach	15	11
Stoma	7	4
Ulcer size (cm)		
Mean	1.8±0.1	1.8±0.6
Range	0.5–3.0	0.5–3.0
Stigmata of hemorrhage (no. of patients)		
Arterial spurting	11	15
Visible vessel	17	18
Oozing	18	16
Adherent clot	64	61

\*There were no significant differences between the groups with regard to the characteristics shown. Plus-minus values are means ±SD. NSAID denotes nonsteroidal antiinflammatory drug.

†Smokers were defined as people who smoked five or more cigarettes per day for more than two years.

bleeding, preexisting medical conditions, use of NSAIDs, *H. pylori* status, ulcer site and size, and stigmata of recent hemorrhage (Table 1).

Continued bleeding or further bleeding was recorded in 12 patients assigned to omeprazole (10.9 percent; 95 percent confidence interval, 5.1 to 16.7 percent) and 40 patients assigned to placebo (36.4 percent; 95 percent confidence interval, 27.3 to 45.3 percent). This difference was significant (odds ratio, 4.7; 95 percent confidence interval, 2.7 to 7.4;  $P<0.001$ ). Continued bleeding was limited to five patients with arterial spurting, two in the omeprazole group and three in the placebo group.

Eight patients in the omeprazole group (7.3 percent; 95 percent confidence interval, 2.5 to 12.2 percent) and 26 patients in the placebo group (23.6 percent; 95 percent confidence interval, 15.7 to 31.5 percent) had surgery to control ulcer bleeding (odds ratio, 3.9; 95 percent confidence interval, 1.7 to 8.5;  $P<0.001$ ). Two patients in the omeprazole group died (1.8 percent; 95 percent confidence interval, -0.6 to 4.3 percent), as compared with six patients in the placebo group (5.5 percent; 95 percent confidence interval, 1.2 to 9.6 percent), a difference that was not significant (odds ratio, 3.1; 95 percent confidence interval, 0.4 to 3.7).

Thirty-two patients receiving omeprazole (29.1 percent; 95 percent confidence interval, 20.8 to 37.2 percent) and 78 receiving placebo (70.9 percent; 95 percent confidence interval, 62.4 to 79.4 percent) received transfusions (odds ratio, 5.9; 95 percent confidence interval, 3.3 to 10.4;  $P<0.001$ ). The mean number of units of blood transfused per patient was  $2.3\pm 1.0$  in the omeprazole group and  $4.1\pm 2.1$  in the placebo group ( $P<0.001$ ). The hospital stays lasted  $5.5\pm 2.1$  days and  $6.9\pm 2.1$  days, respectively ( $P=0.01$ ).

The major outcomes (further bleeding, surgery, and death) are shown in Table 2 according to study group and stigmata of ulcer-related hemorrhage at the time of randomization. The rates of recurrent bleeding and surgery in the placebo group varied considerably with the stigmata. Omeprazole therapy was associated with significant reductions in both further bleeding and surgery among patients with nonbleeding, visible vessels and adherent clots, but not among those with arterial spurting or oozing.

Table 3 shows the effects of covariables on the rate of further bleeding in the two groups combined, as determined by logistic-regression analysis. A hemoglobin concentration of 10 g per deciliter or less, a systolic blood pressure of 100 mm Hg or less on admission, and an ulcer size of 1 cm or larger were all associated with an increased rate of further bleeding. We obtained similar results when we analyzed each study group separately (data not shown).

Two hundred fifteen patients underwent endoscopy a second time, and there was evidence of further bleeding in 47 patients; nonbleeding, visible vessels in 21; persisting black, sloughing clots in 51; flat red spots in 80; and a clean ulcer base in 16. Of the 125 ulcers with adherent clots on initial endoscopy, 51 (26 in the omeprazole group and 25 in the placebo group) had black, sloughing clots covering the ulcer on the second examination, whereas 74 (38 and 36, respectively) had flat red spots over the base of the ulcer. Sixty patients in the omeprazole group (54.5 percent) had clean ulcer bases or ulcers with flat, pigmented spots, as compared with 36 patients in the placebo group (32.7 percent,  $P<0.001$ ).

All eight patients who died were patients who had

undergone surgery. The cause of death was continued bleeding in four patients, chronic renal failure in two, pulmonary embolism in one, and chronic obstructive pulmonary disease in one.

### DISCUSSION

We studied patients who had endoscopically confirmed peptic ulcers with evidence of recent hemorrhage. In patients treated medically, rates of further bleeding vary with the endoscopic findings and have been reported as follows: 88 percent in patients with arterial spurting,<sup>4</sup> 50 percent in patients with visible vessels,<sup>4</sup> 33 percent in patients with adherent clots,<sup>4</sup> and 31 percent in patients with oozing ulcers.<sup>19</sup> In our study, the rates of further bleeding in the placebo group among patients with these findings were 93.3 percent, 55.6 percent, 21.3 percent, and 18.8 percent, respectively. None of our patients received H<sub>2</sub>-receptor antagonists. Under similar conditions, omeprazole given at a dose of 40 mg every 12 hours in 10 patients maintained the median gastric pH (when readings were taken every 10 minutes for 24 hours) at a level of 5.9 to 7.2, as compared with 0.7 to 3.5 in a placebo group (unpublished data). Ninety-eight percent of the pH readings in the patients treated with omeprazole were higher than 6.8. Lanas et al.<sup>23</sup> recorded the intragastric pH in 10 patients with duodenal ulcers that were not bleeding actively after treating the patients with intravenous omeprazole (an 80-mg bolus dose followed by 40 mg every 12 hours) and found that the gastric pH was high (greater than 6) most of the time, being less than 6 during 15 percent of the first 24-hour period after omeprazole treatment was started.<sup>23</sup> The parietal-cell mass in duodenal ulcers is much lower in Indian patients than in those in Western countries,<sup>24,25</sup> which may explain the increased response to omeprazole in our patients as compared with those studied by Lanas et al.

We found that omeprazole therapy was associated with significant reductions in the rates of further bleeding and surgical intervention, the number of days in the hospital, and the need for transfusion. These findings contrast with those of a large, randomized trial that did not show a treatment-associated benefit of omeprazole.<sup>26</sup> However, that study included all patients with acute gastrointestinal bleeding, regardless of the cause of bleeding or the risk factors; thus, the possible benefit of treatment in patients with recent hemorrhage could have been diluted by the inclusion of a large number of patients at low risk of bleeding. Reports of the use of omeprazole in patients with peptic-ulcer bleeding and stigmata of recent hemorrhage have shown benefits with regard to the rate of further bleeding, the need for transfusion, the number of operations, and the need for endoscopic treatment.<sup>27,28</sup> The benefit of omeprazole was limited to patients with visible ves-

**TABLE 2.** MAJOR OUTCOMES IN THE STUDY PATIENTS WITH BLEEDING PEPTIC ULCERS, ACCORDING TO STIGMATA OF RECENT HEMORRHAGE.

OUTCOME AND STIGMATA	OMEPRAZOLE (N = 110)	PLACEBO (N = 110)
	no. with outcome/no. with stigmata (%)	
Further bleeding		
Spurting	8*/11 (72.7)	14†/15 (93.3)
Visible vessel	2/17 (11.8)	10/18 (55.6)‡
Oozing	2/18 (11.1)	3/16 (18.8)
Clot	0/64	13/61 (21.3)§
Surgery		
Spurting	6/11 (54.5)	11/15 (73.3)
Visible vessel	1/17 (5.9)	8/18 (44.4)‡
Oozing	1/18 (5.6)	1/16 (6.3)
Clot	0/64	6/61 (9.8)‡
Death		
Spurting	1/11 (9.1)	3/15 (20.0)
Visible vessel	1/17 (5.9)	2/18 (11.1)
Oozing	0/18	0/16
Clot	0/64	1/61 (1.6)

\*Two of the eight patients had continued bleeding.

†Three of the 14 patients had continued bleeding.

‡P = 0.02 for the comparison with the omeprazole group.

§P < 0.001 for the comparison with the omeprazole group.

**TABLE 3.** LOGISTIC-REGRESSION ANALYSIS OF THE EFFECTS OF COVARIABLES ON THE RATE OF FURTHER BLEEDING.\*

COVARIABLE	NO. WITH FURTHER BLEEDING	NO. STUDIED	PERCENT	ODDS RATIO (95% CONFIDENCE INTERVAL)
Age				
>55 yr	38	141	27.0	1.7 (0.9–2.8)
≤55 yr	14	79	17.7	
Systolic blood pressure				
≤100 mm Hg	27	81	33.3	2.3 (1.4–3.7)
>100 mm Hg	25	139	18.0	
Hemoglobin				
≤10 g/dl	50	160	31.2	13.2 (3.5–32.1)
>10 g/dl	2	60	3.3	
NSAID use				
Yes	13	37	35.1	1.6 (0.8–3.4)
No	39	183	21.3	
Ulcer site				
Stomach	9	26	34.6	1.6 (0.8–4.7)
Duodenum	43	183	23.5	
Ulcer size				
>1 cm	46	156	29.5	3.8 (1.6–9.1)
≤1 cm	6	64	9.4	

\*Data shown are based on all 220 patients in both study groups combined. NSAID denotes nonsteroidal antiinflammatory drug.

sels and adherent clots and was not found in patients with arterial spurting. The results of endoscopic treatment in the latter are more favorable.<sup>4-7</sup> Hemostasis was initially achieved in a large proportion of such patients (more than 90 percent) by thermal contact with both bipolar electrocoagulation and heater-probe therapy, but rates of further bleeding and emergency surgery were significantly reduced only in the patients treated with heater probes. The results of combination therapy (an injection of epinephrine plus either bipolar electrocoagulation or heater-probe therapy) were better than those of a single endoscopic treatment.

Endoscopic therapy, if available, should be instituted at the beginning of treatment in patients with arterial spurting. Surgery should be considered only if this treatment fails to control bleeding. It is important to remember that the results of our study may not be generalizable to patients in the United States and other developed countries, where endoscopic therapy is commonly used in patients with bleeding and those with nonbleeding, visible vessels. Moreover, we did not study the potential benefit of combining omeprazole with endoscopic therapy.

Mortality from bleeding peptic ulcers has remained constant, at 5 to 10 percent, in a large number of series described over the past six decades.<sup>1</sup> This is possibly due to an increasing proportion of patients over the age of 60, many of whom have complicated underlying illnesses. Patients with preexisting medical conditions, those with uncontrolled or recurrent bleeding, and those undergoing surgery — particularly when such patients are over 60 — are at high risk of death. Our findings support the use of potent acid suppression, with high doses of proton-pump inhibitors, in patients with bleeding peptic ulcers.

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