

ENDOSCOPIC RETREATMENT COMPARED WITH SURGERY IN PATIENTS WITH RECURRENT BLEEDING AFTER INITIAL ENDOSCOPIC CONTROL OF BLEEDING ULCERS

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ABSTRACT

Background and Methods After endoscopic treatment to control bleeding of peptic ulcers, bleeding recurs in 15 to 20 percent of patients. In a prospective, randomized study, we compared endoscopic retreatment with surgery after initial endoscopy. Over a 40-month period, 1169 of 3473 adults who were admitted to our hospital with bleeding peptic ulcers underwent endoscopy to reestablish hemostasis. Of 100 patients with recurrent bleeding, 7 patients with cancer and 1 patient with cardiac arrest were excluded from the study; 48 patients were randomly assigned to undergo immediate endoscopic retreatment and 44 were assigned to undergo surgery. The type of operation used was left to the surgeon. Bleeding was considered to have recurred in the event of any one of the following: vomiting of fresh blood, hypotension and melena, or a requirement for more than four units of blood in the 72-hour period after endoscopic treatment.

Results Of the 48 patients who were assigned to endoscopic retreatment, 35 had long-term control of bleeding. Thirteen underwent salvage surgery, 11 because retreatment failed and 2 because of perforations resulting from thermocoagulation. Five patients in the endoscopy group died within 30 days, as compared with eight patients in the surgery group ($P=0.37$). Seven patients in the endoscopy group (including 6 who underwent salvage surgery) had complications, as compared with 16 in the surgery group ($P=0.03$). The duration of hospitalization, the need for hospitalization in the intensive care unit and the resultant duration of that stay, and the number of blood transfusions were similar in the two groups. In multivariate analysis, hypotension at randomization ($P=0.01$) and an ulcer size of at least 2 cm ($P=0.03$) were independent factors predictive of the failure of endoscopic retreatment.

Conclusions In patients with peptic ulcers and recurrent bleeding after initial endoscopic control of bleeding, endoscopic retreatment reduces the need for surgery without increasing the risk of death and is associated with fewer complications than surgery. (*N Engl J Med* 1999;340:751-6.)

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BLEEDING peptic ulcer is a life-threatening emergency with a mortality rate of around 10 percent.^{1,2} Endoscopic therapy is the first treatment to control hemorrhage, and it improves the outcome for patients.^{3,4} In 15 to 20 percent of patients, bleeding recurs after hemostasis has been established by endoscopy. Such patients are often elderly and at high surgical risk, and they are likely to benefit if endoscopy is repeated with satisfactory results. Conversely, the hypotension and delay in reestablishing hemostasis that result from repeated but unsuccessful endoscopic attempts are likely to adversely affect their survival. We compared endoscopic retreatment with surgery in patients in whom bleeding recurred after initial endoscopic control of bleeding peptic ulcers.

METHODS

Design and Protocol of the Study

The protocol for this prospective, randomized trial was approved by the ethics committee of the faculty of medicine of the Chinese University of Hong Kong and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients or their next of kin.

From December 1994 to April 1998, a total of 3473 adults with bleeding peptic ulcers were admitted to the Prince of Wales Hospital. All patients were jointly cared for by medical and surgical gastroenterologists according to a standard protocol. All patients underwent endoscopy within 12 hours after admission. Patients with circulatory instability and those who were vomiting fresh blood on admission underwent emergency endoscopy.

Endoscopic therapy was performed with the use of topical pharyngeal anesthesia supplemented by intravenous emulsified diazepam (Diazemuls, Pharmacia & Upjohn, Stockholm, Sweden). A twin-channel endoscope (model GIF-2T-200, Olympus, Tokyo, Japan) was used for actively bleeding ulcers and ulcers with non-bleeding visible vessels. Clots on ulcer floors were lifted, and underlying vessels were treated when present. Ulcers were first injected with epinephrine (dilution, 1:10,000) in aliquots of 0.5 to 1 ml with a 21-gauge needle. Coaptive thermocoagulation, which involves the compression of two vessel walls, was then applied to the vessel with a 3.2-mm heater probe (model CD-10Z, Olympus) at 30 J. A minimum of three continuous pulses was applied. Hemostasis was considered to have been established and endoscopy successful if active bleeding stopped and there was flattening, or cavitation, of bleeding vessels. Antral-biopsy specimens were obtained

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to determine whether *Helicobacter pylori* was present with the use of a rapid urease test (CLO test, Delta West, Bentley, Australia).

After treatment, patients were returned to a surgical ward for monitoring. Intravenous acid-suppression agents were not routinely prescribed. A policy of early initiation of oral feeding and medication was followed. A one-week course of oral omeprazole (Losec, Astra, Mölndal, Sweden), amoxicillin (Amoxil, Bristol-Myers Squibb, Sermoneta, Italy), and clarithromycin (Klacid, Abbott, Kent, United Kingdom) was given if the rapid urease test was positive, and a four-week course of oral omeprazole was given if the test was negative. The hemoglobin level was checked daily, and transfusions were given when necessary to maintain the hemoglobin level at 10 g per deciliter or higher.

Bleeding was considered to have recurred in the event of any of the following: vomiting of fresh blood, the development of hypotension (defined as systolic blood pressure of 90 mm Hg or less or a pulse rate of 110 per minute or more) and melena, or a requirement for more than four units of blood in the 72-hour period after endoscopic treatment. Patients who satisfied any of these criteria were eligible for the trial. Only patients who were dying of cancer were excluded. When a patient was judged by his or her physician to have recurrent bleeding, the physician contacted one of the investigators or the research office at the department of surgery. Once the patient's eligibility was verified, the patient was randomly assigned by means of an opaque, sealed envelope to undergo either endoscopic retreatment or surgery. The patient was then immediately transferred to the endoscopy suite or operating room, depending on the treatment assigned. For patients assigned to endoscopic retreatment, the combination of epinephrine injection and thermocoagulation was again used. For those assigned to surgery, the choice of operation was left to the surgeon. Intravenous treatment with 40 mg of omeprazole every 12 hours was given to patients after endoscopic retreatment and to those in the surgery group who underwent simple ulcer plication or excision alone until they resumed an oral diet.

Outcome variables included the duration of hospitalization after treatment, the need for hospitalization in the intensive care unit, the need for blood transfusion, treatment-related complications, and 30-day mortality. Treatment-related complications included any complications that developed after endoscopic retreatment and subsequent salvage surgery.

Statistical Analysis

The rate of death related to failed endoscopic treatment ranges from 15 to 25 percent.⁵⁻⁷ Data are lacking on mortality rates after endoscopic retreatment and after salvage surgery for failed endoscopy. We estimated that approximately 30 percent of patients who were admitted with bleeding ulcers would require endoscopic treatment. If the rate of recurrent bleeding is assumed to be 10 percent among those treated, then a pool of 3000 patients would be required to recruit 90 patients into this trial. A minimum of 42 patients was required in each group for the study to have a power of 80 percent to detect an absolute reduction of 30 percent (from 45 percent to 15 percent) in mortality with a type I error of 5 percent (two-sided). The end-point data were analyzed according to the intention-to-treat principle. Fisher's exact test and Pearson's chi-square test were used to analyze categorical data.⁸ Factors that could be used to predict the failure of endoscopic retreatment were identified by univariate analysis. These variables were then entered into a stepwise, multiple logistic-regression analysis.⁹ All P values were two-tailed. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Of the 3473 patients with bleeding peptic ulcers who were admitted to the hospital during the study period, 1169 (33.7 percent) underwent endoscopy to reestablish hemostasis. Hemostasis was not achieved in 17 patients (1.5 percent), and these patients went

directly to surgery. Bleeding recurred in 100 patients (8.7 percent). Six of these patients did not undergo randomization, five because of terminal cancer and one because of cardiac arrest. Two patients with malignant ulcers were excluded after randomization, leaving 92 patients for analysis, 48 of whom were assigned to endoscopic retreatment and 44 to surgery.

Characteristics of the Patients

There were no significant differences between the two groups with respect to demographic characteristics, the site and size of ulcers, the severity of bleeding, and the interval between endoscopy and the recurrence of bleeding (Table 1). Twenty-five patients in each group had hypotension at entry into the trial. The median transfusion requirement before randomization was similar in the two groups (about five units). Patients assigned to surgery had significantly more epinephrine injected (mean volume, 11.1 ml vs. 14.3 ml; $P=0.04$) during the initial endoscopy than those assigned to endoscopic retreatment, but the number of heater-probe pulses used was similar (median, 8 vs. 9; $P=0.35$). More patients had used nonsteroidal antiinflammatory drugs in the endoscopy group than in the surgery group, but the difference was not significant (21 vs. 10, $P=0.05$).

Endoscopic Retreatment

At endoscopy, recurrent bleeding was confirmed in all 48 patients; spurting or oozing hemorrhage was present in 10 patients, and visible vessels or clots together with fresh blood or coffee-grounds material in the stomach were present in the other patients. A mean (\pm SD) of 11.2 ± 5.1 ml of epinephrine was injected, and a median of 12 pulses of the heater probe were applied (range, 3 to 33). Two of the 48 patients had perforations related to the heater probe after endoscopic retreatment (4.2 percent), as compared with 13 of the 1169 patients who underwent initial endoscopy (1.1 percent). Hemostasis could not be achieved in four patients, and pneumoperitoneum developed as a result of ulcer perforation in one patient. These five patients went directly to surgery, and none died. Of the remaining 43 patients, 8 required subsequent salvage surgery. Seven of these eight had recurrent bleeding, and one patient with an anterior duodenal ulcer had an ulcer perforation 24 hours after retreatment. Four of these eight patients died after salvage surgery.

Long-term hemostasis was achieved in 35 patients. Before the six-week follow-up, 1 of these 35 patients (who had an anastomotic ulcer) returned because of minor bleeding and was again treated endoscopically. One patient died of pneumonia.

Surgery

Among the 44 patients who were assigned to undergo surgery, 22 underwent partial gastrectomy, 12

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

CHARACTERISTIC	ENDOSCOPIC RETREATMENT (N=48)	SURGERY (N=44)
Age (yr)	65±17	65±15
Sex (M/F)	37/11	33/11
Concurrent illnesses (no. of patients)	33	24
ASA grade (no. of patients)†		
I	15	20
II	18	8
III	9	12
IV	6	4
Bleeding during hospitalization (no. of patients)	10	6
Hemoglobin at randomization (g/dl)	8.4±2.6	8.4±2.9
Hypotension (no. of patients)‡		
On admission	17	13
At randomization	25	25
Vomiting of fresh blood (no. of patients)		
At presentation	20	17
At recurrent bleeding	20	19
Units of blood transfused before randomization		
Median	4.5	5
Range	1–15	2–8
Interval between endoscopy and recurrent bleeding (hr)		
Median	34	25
Range	3–168	3–216
Endoscopic treatment		
Dose of epinephrine (ml)	11.1±4.7	14.3±6.1§
No. of probe pulses		
Median	8	9
Range	3–35	3–31
Ulcer size (cm)	1.2±0.7	1.4±0.9
Ulcer size ≥2 cm (no. of patients)	10	15
Location of ulcer (no. of patients)		
Duodenum	24	24
Gastrum	17	17
Anastomosis	7	3
Positive rapid urease test (no. of patients)	20	22
NSAID use (no. of patients)¶	21	10
Coagulopathy (no. of patients)	5	7

*Plus-minus values are means ±SD.

†The American Society of Anesthesiology (ASA) grading system indicates the surgical risk, with higher grades indicating higher surgical risk.¹⁰

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

§P=0.04.

¶NSAID denotes nonsteroidal antiinflammatory drug.

underwent vagotomy and pyloroplasty, 8 underwent ulcer plication or simple ulcer excision alone, and 2 patients with anastomotic ulcers after a previous Polya's operation (anastomosis of the transected end of the stomach to the side of the jejunum after subtotal gastrectomy) underwent simple plication with completion of the vagotomy and revision of the partial gastrectomy, respectively. Bleeding recurred postoperatively in three patients: two patients after ulcer excision alone, in whom revision of the partial gastrectomy was required, and one patient after vagotomy and pyloroplasty, in whom bleeding was managed

TABLE 2. OUTCOMES AFTER ENDOSCOPIC RETREATMENT OR SURGERY.

VARIABLE	ENDOSCOPIC RETREATMENT (N=48)	SURGERY (N=44)	P VALUE
Duration of hospitalization (days)			0.59
Median	10	11	
Range	2–111	4–42	
Hospitalization in intensive care unit			0.16
Length of stay (days)	59	59	
No. of patients	5	10	
Units of blood transfused			0.27
Median	8	7	
Range	1–21	3–150	
Complications			0.03
No. of complications	22	28	
No. of patients	7	16	
30-Day mortality (no. of patients)	5	8	0.37
Abdominal sepsis	2	2	
Bronchopneumonia	2	1	
Acute myocardial infarction		2	
Multiorgan dysfunction	1	1	
Hepatic failure		1	
Ventricular arrhythmia		1	

conservatively. Two other patients required repeated laparotomy for abdominal sepsis resulting from a duodenal-stump leak and dehiscence of pyloroplasty. Both these patients died.

Outcome, Morbidity, and Mortality

The duration of hospitalization, the need for hospitalization in the intensive care unit and the resultant duration of that stay, and transfusion requirements were similar in the two groups (Table 2). More complications were observed among the patients in the surgery group than among those assigned to endoscopic retreatment (16 vs. 7; P=0.03; odds ratio, 3.45; 95 percent confidence interval, 1.2 to 9.1). In the endoscopy group, six of the seven patients who had complications had undergone salvage surgery. The complication rate after salvage surgery was 46 percent (occurring in 6 of 13 patients). Anastomotic dehiscence, including duodenal-stump leaks, occurred in two patients in each group (Table 3).

There were no significant differences in 30-day mortality (P=0.37) (Table 2). In the endoscopy group, five patients (10 percent) died within 30 days after the initial endoscopy. Four of these five patients died after salvage surgery. There were eight deaths (18 percent) in the surgery group.

Factors Predicting the Failure of Endoscopic Retreatment

The two patients with perforations caused by thermocoagulation were excluded from the analysis of factors that could be used to predict the failure of endoscopic retreatment. Thus, there were 35 patients in the group with successful long-term hemostasis

TABLE 3. COMPLICATIONS WITHIN 30 DAYS AFTER ENDOSCOPIC RETREATMENT OR SURGERY.*

COMPLICATION	ENDOSCOPIC RETREATMENT (N=48)†	SURGERY (N=44)
	no. of complications	
Respiratory failure‡	3 (3)	5
Acute myocardial infarction	0	3
Cardiac arrhythmia	0	2
Stroke	1 (1)	1
Nosocomial pneumonia	4 (3)	5
Wound-related complications (dehiscence or infection)	2 (2)	1
Hepatic failure		1
Acute renal failure	1 (1)	3
Abdominal sepsis		
Duodenal-stump leak	1 (1)	2
Dehiscence after pyloroplasty	1 (1)	
Thermocoagulation-induced perforation	2	
Small-bowel ischemia		1
Recurrent bleeding	7	3
Tension pneumothorax		1
Total no. of complications	22 (12)	28

*Complications occurred in 7 patients after endoscopic retreatment, 6 of whom had complications as a result of salvage surgery after unsuccessful endoscopic retreatment, and in 16 patients after surgical treatment.

†Values in parentheses are the numbers of complications that occurred after salvage surgery for unsuccessful endoscopic retreatment.

‡Respiratory failure was defined as the need for ventilatory assistance for more than four days or the need for a tracheostomy.

and 11 patients in the group for which endoscopic retreatment was unsuccessful. The two groups were similar with respect to age, ratio of men to women, the site and size of ulcers, and transfusion requirements before randomization and after treatment (Table 4). The numbers of patients with high-risk ulcers were also similar. Patients for whom endoscopic retreatment was unsuccessful were more likely to have hypotension at randomization ($P=0.004$) and to have larger ulcers — at least 2 cm ($P=0.04$). All the patients for whom retreatment was unsuccessful had other illnesses, as compared with 22 of the patients for whom endoscopic retreatment was successful ($P=0.02$ by Fisher's exact test). When these variables were entered into a stepwise, multiple logistic-regression analysis, hypotension ($P=0.01$) and an ulcer size of at least 2 cm ($P=0.03$) remained significant independent factors predictive of the failure of endoscopic retreatment.

DISCUSSION

Our trial was conducted in a specialized center with expertise in controlling bleeding peptic ulcers

endoscopically. Our 8.7 percent rate of recurrent bleeding after initial endoscopy was attributed to the use of a team approach, a defined management protocol, and aggressive endoscopic treatment with combination therapy for actively bleeding ulcers and ulcers with major stigmata of bleeding, including adherent clots. In a previous randomized study, we demonstrated that the combination of epinephrine injection and thermocoagulation was more effective than epinephrine injection alone.¹¹

Extrapolation of our results to other centers where endoscopic treatment is not administered as effectively may not be warranted. Repeated, unsuccessful attempts to restore hemostasis endoscopically could compromise the survival of patients. Salvage surgery for recurrent bleeding is associated with a mortality rate ranging from 15 to 25 percent.⁵⁻⁷ There is little information on the outcome of patients after endoscopic retreatment for recurrent bleeding. In our study, however, the mortality rate was less than 20 percent.

Endoscopic retreatment led to long-term hemostasis in about three quarters of the patients who had recurrent bleeding. This approach reduces the need for surgery (with attendant morbidity) without increasing mortality. Our findings challenge the view that surgery is mandatory in patients with peptic ulcers that bleed again after initial endoscopic control. Our analysis indicates that endoscopic retreatment of smaller ulcers in patients with relatively stable hemodynamics has a high rate of success. For patients with larger ulcers and therefore heavier bleeding, surgery may be a better choice than endoscopic retreatment. A logical approach in patients with larger ulcers might be to perform elective surgery before bleeding recurs, since there were substantial complications after emergency salvage surgery in these patients. In addition, the eradication of *H. pylori* prevents recurrence of ulcers and bleeding complications.¹²⁻¹⁴

The success of endoscopic retreatment depends to a large extent on the size of the bleeding vessel itself. Arteries in smaller ulcers are mostly submucosal and have a mean diameter of 0.5 mm. In larger, chronic ulcers, the eroded arteries are serosal and have a mean diameter of 0.9 mm.¹⁵ In a canine model, coaptive thermocoagulation was consistently effective in arteries that were less than 2.0 mm in diameter.¹⁶ In a clinical endoscopic setting, however, vessels that are larger than 1.0 mm in diameter may be difficult to seal. The median size of the bleeding arteries in our patients with recurrent bleeding was 1.0 mm (range, 0.4 to 1.35). In smaller ulcers, recurrent bleeding is usually a consequence of inadequate thermocoagulation initially, and endoscopic retreatment is worthwhile. In our study, 11 patients with high-risk ulcers located at the posterior duodenal bulb or angular notch underwent endoscopic retreatment, and long-term hemostasis was achieved in 7. Erosion into ma-

TABLE 4. FACTORS PREDICTING THE FAILURE OF ENDOSCOPIC RETREATMENT OF BLEEDING ULCERS.*

VARIABLE	SUCCESSFUL LONG-TERM HEMOSTASIS (N=35)	UNSUCCESSFUL LONG-TERM HEMOSTASIS (N=11)	UNIVARIATE ANALYSIS		MULTIPLE LOGISTIC- REGRESSION ANALYSIS	
			P	ODDS RATIO	P	ODDS RATIO
			VALUE	(95% CI)	VALUE	(95% CI)
Age (yr)	64.8±17.7	68.5±15.8	0.52	1.01 (1.0–1.1)		
Sex (M/F)	27/8	8/3	1.0	0.79 (0.2–3.7)		
Bleeding during hospitalization (no. of patients)	5	4	0.19	3.43 (0.7–16.2)		
Coexisting illnesses (no. of patients)†	22	11	0.02			
NSAID use (no. of patients)	16	4	0.73	0.68 (0.2–2.7)		
Coagulopathy (no. of patients)	3	2	0.58	2.37 (0.3–16.4)		
Hemoglobin (g/dl)	8.0±2.2	7.6±2.0	0.57	0.91 (0.6–1.3)		
Units of blood transfused before randomization	4.7±3.2	5.2±1.5	0.59	1.06 (0.8–1.3)		
Hypotension (no. of patients)						
On admission	11	5	0.48	1.82 (0.5–7.3)		
At randomization	13	10	0.004	16.9 (1.9–147)	0.01	32.6 (2.3–454)
Location of ulcer (no. of patients)			0.95			
Duodenum	17	5				
Gastrum	13	4				
Anastomosis	5	2				
Ulcer size, ≥2 cm (no. of patients)	5	5	0.04	5.0 (1.1–22.8)	0.03	12.2 (1.2–121)
High-risk ulcers (no. of patients)	7	4	0.42	2.29 (0.5–10.1)		
Angular incisural ulcer	3	1				
Lesser-curve gastric ulcer	2	2				
Posterior duodenal ulcer	2	1				

*Two patients with perforations induced by thermocoagulation were excluded from the analysis. Plus-minus values are means ±SD. CI denotes confidence interval, and NSAID nonsteroidal antiinflammatory drug.

†The odds ratio could not be calculated because the value in one of the cells was zero.

for arteries such as the gastroduodenal arteries and the left gastric arteries is uncommon, and in such cases it is unlikely that hemostasis would have been achieved at initial endoscopy.

Two patients had perforations related to the heater probe. In both patients, the ulcers were in the thin anterior wall of the duodenum. The heater probe can be used with greater safety at other sites in the gastroduodenal tract and, paradoxically, for chronic ulcers, which are often firmly attached to surrounding structures by a thick, fibrous tissue.

The rate of complications after salvage surgery was substantial: 36 percent when surgery was performed after the initial endoscopy and 46 percent when it was performed after the second endoscopy. The use of intravenous antisecretory drugs after endoscopic control of bleeding ulcers remains controversial. Recent evidence suggests that high-dose oral or intravenous omeprazole can reduce the risk of recurrent bleeding and may represent an important adjunct to endoscopic therapy.^{17,18} Alternative strategies of reducing the need for surgery include routine follow-up (“second look”) endoscopy and prophylactic retreatment. The results of randomized studies have been

limited by the inclusion of small numbers of patients or the use of suboptimal treatment at primary endoscopy.^{19–22} In a recent large trial, daily endoscopy and treatment with fibrin glue reduced the incidence of recurrent bleeding.²³ Daily endoscopy is, however, uncomfortable for patients and costly. Its benefits are likely to be marginal if the effectiveness of the initial treatment is increased. Scheduled retreatment may nonetheless be of value in selected high-risk patients.²⁴ The use of a different endoscopic therapy once bleeding recurs also remains an option. There has, however, been no randomized study comparing the use of contact thermal devices, fibrin sealant, and hemoclips.

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