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Oral Omeprazole in Patients Undergoing Combination Endoscopic Therapy for Bleeding Peptic Ulcers: A Prospective Double-Blind Randomized Study

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ABSTRACT

Background

Endoscopic therapies can decrease the morbidity of patients with high risk peptic ulcer. The aim of this study was to evaluate the beneficial effects of oral omeprazole therapy in patients with bleeding peptic ulcer who received combined endoscopic treatment (epinephrine injection and Argon Plasma Coagulation).

Materials and Methods

Eighty six patients with bleeding from gastric, duodenal or stomal ulcers and endoscopic stigmata of recent bleeding were enrolled in our study. All patients received injection of epinephrine (1:10,000) and also their ulcers were treated with Argon Plasma Coagulator. The patients then randomly assigned to receive oral omeprazole (40 mg every 12 hours) or placebo.

Results

Five (11.6%) of 43 patients in the placebo group had rebleeding; but no rebleeding was detected among 43 patients in omeprazole group (p= 0.05). One patient in the Placebo group underwent surgery for control of his rebleeding; but none of the patients in omeprazole group needed surgery. One patient in the placebo group and none of the patients in the omeprazole group died. The average hospital stay was 5 days in the omeprazole group and 5.8 days in the placebo group.

Conclusions

Addition of oral omeprazole to combined endoscopic therapy significantly reduces recurrent bleeding rates.

Keywords: Upper GI bleeding, Omeprazole, Argon plasma coagulation, Endoscopic therapy
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BACKGROUND

Although high rates of initial hemostasis can be achieved with endoscopic combined therapy in actively bleeding ulcers, the incidence of

rebleeding remains significant. After endoscopic treatment of bleeding peptic ulcers; bleeding may recur in up to 15-20% of patients.(1, 2), Optimal conditions for clotting may require achieving adequate and sustained acid inhibition to avoid the deleterious effect of acid and pepsin secretions on the hemostatic process. A blood clot in a peptic ulcer is unstable in a low pH environment. Use of high dose intravenous omeprazole will reduce the frequency of rebleeding after endoscopic treatment of bleeding peptic ulcers.(3), While PPIs★ have been accessible in intravenous formulations in several European countries, they have been available only as oral drugs in developing countries like Iran. Oral preparations are significantly cheaper than the intravenous formulas, there are few studies on the effectiveness of oral PPIs in the setting of bleeding peptic ulcers. None of these studies have used the combined endoscopic therapy and specifically APC★★ for treating the bleeding peptic ulcers.

We designed this study to address the question of whether oral omeprazole has any added benefit following achievement of hemostasis of bleeding peptic ulcers with combined endoscopic epinephrine injection and APC.

MATERIALS AND METHODS

Patients

This study was conducted in a tertiary referral center in Tehrn (endoscopic unit of DDRC★★★ in Shariati hospital, Tehran, Iran). Over an eighteen months period, from December 2001 to June 2003, all patients presenting with acute upper gastrointestinal bleeding were considered for inclusion in the study if gastroenterology fellows witnessed hematemesis, melena, or bloody nasogastric aspirate. After fluid resuscitation, the patients underwent upper gastrointestinal endoscopy within 12 hours of admission. Patient with duodenal, gastric, or stomal ulcers and endoscopic stigmata of recent bleeding were enrolled in our study. Endoscopic stigmata of recent bleeding consisted of spurting artery, presence of a visible vessel with or without active bleeding, presence of an adherent clot, or ulcer with actively oozing of blood. Exclusion criteria included: malignant bleeding ulcers; severe comorbidities contraindicating conscious sedation and endoscopy; massive bleeding precluding the possibility of endoscopic visualization and endoscopic hemostasis; and continued bleeding within the first 4 hours of endoscopic treatment necessitating emergent surgery.

Study design

This study was designed as a randomized controlled prospective double-blinded trial. Patients underwent upper gastrointestinal endoscopy within the first 12 hours after hospital admission and received epinephrine injection and argon plasma coagulation (APC) therapy. Upper gastrointestinal endoscopy was performed in standard fashion with a video Olympus esophagogastroduodenoscope. Epinephrine (1:10,000 dilution) in 1-2 ml aliquots was injected with a flexible needle injector (Marcon-Haber 23-gauge needle, Wilson-Cook Medical, Winston-Salem, N.C.) into the submucosa in each quadrant at the edge of ulcer and also directly into the ulcer base and around the bleeding or nonbleeding visible vessel until all bleeding stopped. At least 8 mL of epinephrine were injected. Then patients underwent treatment with an argon plasma coagulator unit (APC-300 and ICC-350, Erbe, Tubingen, Germany). Spray mode was used with 2 power/gas settings (respectively, 40 and 70 W and 1.5 to 3 L/min). Probes of 2.3 mm and 3.5 mm were used with endoscopes according to corresponding channel diameters. Continuous suction was applied to remove smoke and prevent overinflation of the GI tract. Two biopsy specimens were obtained from the gastric antrum for rapid urease test (RUT) and histopathologic evaluation.

Patients were randomly assigned to receive

★ Proton Pomp Inhibitors
★★ Argon Plasma Coagulation
★★★ Digestive Disease Research Center

omeprazole or an identical-looking placebo (both of them provided by Lorestan Pharmaceutical Corporation). Randomization was carried out in DDRC department using sealed opaque envelopes labeled with a code known to only one of the senior DDRC researcher. The endoscopist, physician, patients, and other medical personnel were blinded to study group. According to random assignment, the patient received either oral omeprazole (40 mg every 12 hours) or placebo for 5 days. No other treatment was allowed. The study was conducted in a double-blinded manner. All patients provided written informed consent. The study was approved by the ethic committee of Digestive Disease Research Center, Tehran University of Medical Sciences. Every patient was serially monitored for vital signs and hemoglobin concentration, need for blood transfusion, and need for surgery. Demographic features, comorbid illnesses, ulcer size, smoking status, use of NSAIDs★ and *Helicobacter pylori* status as determined by enzyme-linked immunosorbent assay (ELISA), rapid urease test, and histopathologic evaluation of antral mucosal biopsy specimen were recorded.

The treatment protocol was continued for a total of 5 days after the endoscopic treatment. After the fifth day, patients who were *H. pylori* infected received triple therapy for 2 weeks and omeprazole 20 mg daily for 4 or 8 weeks according to the location of their ulcers (duodenal ulcer or gastric ulcer respectively), and patients who were not infected received only omeprazole 20 mg daily for 4 or 8 weeks as mentioned above, irrespective of the treatment protocol. Patients who had special risk factors such as need for continuous NSAID use were approached individually for prevention of long term gastrointestinal complication.

After early stabilization of pulse, blood pressure, and hemoglobin concentration; recurrent bleeding was defined by hematemesis, melena, or both with either shock (pulse rate>100 beats/min, systolic blood pressure <90 mmHg accompanied by cold sweats, pallor and oliguria) or a decrease in hemoglobin concentration of >2g/dl over a 24 hour period. Rebleeding was initially managed with conservative therapy and endoscopic combined therapy, but surgery was indicated when the patient's condition did not stabilized. In addition to failure of endoscopic retreatment, other indications for surgery were as follows: hemodynamic instability despite vigorous resuscitation (>3 unit transfusion); shock associated with rebleeding; continued slow bleeding with a transfusion requirement >3-4 units/day.

The primary end point of the study was the rate of rebleeding. Secondary end points were the mortality rate, duration of hospital stay, and the need for surgery.

★ Non-Steroidal Anti-Inflammatory Drugs

Statistical analysis

Quantitative data are represented as mean ± standard deviation (SD). The Student *t* test was used to compare means between groups. All tests of significance were two-tailed and a p value of less than 0.05 was considered significant. The chi-squared test and Fisher's exact test for proportions were used, where appropriate.

RESULTS

During the study period; 98 patients with duodenal, gastric, or stomal ulcers presented with upper gastrointestinal bleeding accompanied with endoscopic stigmata of recent bleeding. Three patients were excluded from the study because of failure of endoscopic therapy in control of their bleeding. Two patients were excluded after we received the pathologic reports of malignant ulcers. Also 7 patients were excluded from the study due to poor compliance and refusing to sign the consent form. Thus, a total of 86 patients were included in our study. Spurting artery were seen in 6 patients (7%), visible vessel with active bleeding in 16 (18.6%), non-bleeding visible vessel in 13 (15.1%), adherent clot ± oozing ulcer in 13 (15.1%), and oozing ulcer in 38 (44.1%) patients.

Randomization resulted in 43 patients in the omeprazole group and 43 patients in the placebo group. Both groups were comparable to each other with respect to age, sex, clinical presentation, pulse rate, blood pressure, initial hemoglobin concentration, comorbid illness, *H. pylori* status, NSAID intake, site of ulcer, smoking status, and endoscopic stigmata of recent bleeding (Tables 1 and 2). Six patients in the placebo group and one patient in the omeprazole group were warfarin users; but none of these seven warfarin users were developed rebleeding.

Our patients had high rate of comorbid illness. The most common comorbidity was cardiovascular comorbidity which was seen in 21 (48.8%) and 22 (51.2%) patients in omeprazole

Table 1. Baseline characteristics of study patients

Characteristics	Omeprazole Group (n: 43)	Placebo Group (n: 43)
Age ± SD (years)	52.3 ± 19.5	53.9 ± 20.1
Male sex	31 (72.1%)†	36 (83.7%)
Smokers	10 (23.3%)	6 (14.0%)
Warfarin users	1 (2.3%)	6 (14.0%)
NSAID users	21 (48.8%)	19 (44.2%)
Initial hemoglobin (g/dl)	9.7 ± 3.3	10.5 ± 3.5
Orthostatic changes at presentation	10 (23.3%)	8 (18.6%)
Frank hypotension at presentation	6 (14.0%)	6 (14.0%)
Shock at presentation	1 (2.3%)	1 (2.3%)
Positive rapid urease test	17 (39.5%)	17 (39.5%)
Positive histology for *H. pylori*	24 (60.0%)	27 (64.3%)
Positive ELISA (IgG) for *H. pylori*	29 (69.0%)	31 (75.6%)
Positive ELISA (IgA) for *H. pylori*	14 (35.9%)	21 (55.3%)
Positive for *H. pylori* by at least one test	37 (86%)	41 (95.3%)
Previous history of peptic ulcer disease	12 (27.9%)	10 (23.3%)

† Number (%)

Table 2. Ulcer characteristics in study patients

Ulcer characteristics	Omeprazole Group (n: 43)	Placebo Group (n: 43)
Ulcer size ± SD (mm)	11.8 ± 6.6	12.3 ± 7
Duodenal ulcers	22 (51.2%)†	30 (69.8%)
Gastric ulcers	20 (46.5%)	13 (30.2%)
Stomal ulcers	1 (2.3%)	0 (0.0%)
Spurting artery	3 (7.0%)	3 (7.0%)
Visible vessel + active bleeding	8 (18.6%)	8 (18.6%)
Non-bleeding visible vessel	7 (16.3%)	6 (14.0%)
Adherent clot ± active bleeding	5 (11.6%)	8 (18.6%)
Oozing ulcer	20 (46.5%)	18 (41.9%)

† Number (%)

and placebo groups respectively. Also pulmonary, renal, neurologic, hepatic, and cancer comorbidities were seen respectively in 1 (2.3%), 3 (7.0%), 4 (9.3%), 1 (2.3%), and 2 (4.7%) patients in omeprazole group and 2 (4.7%), 3 (7.0%), 5 (11.6%), 1 (2.3%), and 3 (7.0%) patients in placebo group.

Recurrent bleeding was recorded in none of the patients in the omeprazole group, but five (11.6%) patients in the placebo group (OR= 2.13; 95%CI: 1.69-2.69; p= 0.05) (Table 3). All of the rebleedings were occurred during the first three days of hospitalization. Surgical interventions were recorded in none of the patients in the omeprazole group, but one (2.3%) patient in the placebo group. No patient in the omeprazole group, but one patient in the placebo group died. The average hospital stay was 5 ± 0 days in the omeprazole group and 5.8 ± 3.9 days in the placebo group.

In subgroup analysis, rebleeding was observed in none of the patients with spurting artery in the omeprazole group compared with two patients in the placebo group. None of the patients with visible vessel and active bleeding in the omeprazole group had recurrent bleeding, compared with two patients in the placebo group. No patient in the omeprazole or placebo group with non-bleeding visible vessel had rebleeding. None of the patients with adherent clot in the omeprazole group had recurrent bleeding, compared with one patient in the placebo group. No patient in the omeprazole and placebo group with actively bleeding ulcer had rebleeding.

DISCUSSION

Although endoscopic therapy achieves initial hemostasis in more than 90% of cases; the incidence of rebleeding is high (10-20%). Rebleeding after initial, successful hemostasis is the most important factor predicting a poor prognosis; therefore, measures most likely to further improve outcome will be aimed at preventing rebleeding. Our prospective randomized trial was designed to ascertain whether omeprazole therapy after initial endoscopic hemostasis might further reduce rebleeding rates.

In our study, adding oral omeprazole to endoscopic therapy significantly reduced rebleeding rates among patients with high risk bleeding peptic ulcers compared with endoscopic therapy alone. The other variables, such as need for surgery, mortality rates, and hospital stay showed a numerical but statistically insignificant, difference in favor of the omeprazole group.

In previous controlled trials evaluating the effect of oral omeprazole in bleeding peptic ulcers, rebleeding rate has ranged between 7% and 12% in the omeprazole arm of the studies.(4, 5), But in our study, rebleeding rates was 0% in the omeprazole group. This may be due to the fact that in the previous trials only injection sclerotherapy was

Table 3. Outcomes of treatment in study patients

Outcomes	Omeprazole Group (n: 43)	Placebo Group (n: 43)	p value
Hospital stay ± SD (days)	5.0 ± 0.0	5.8 ± 3.9	NS*
Transfusion required ± SD (units)	3.2 ± 3.7	2.4 ± 2.3	NS
Rebleeding	0 (0.0%) †	5 (11.6%)	0.05
Surgery required	0 (0.0%)	1 (2.3%)	NS
Death	0 (0.0%)	1 (2.3%)	NS

† Number (%)

* not significant

used as an endoscopic therapy, but in our study we used epinephrine injection together with APC. Thus, rebleeding rate was also relatively low in the placebo group (11.6%), but adding omeprazole reduced this to 0%. These better outcomes are more conspicuous when we consider the significantly higher prevalence of comorbid illness in our patients (Shariati hospital is a well known tertiary referral center in Iran). We believed that another controlled trial will be needed to ascertain whether APC with epinephrine injection together with oral omeprazole would be a more efficacious therapeutic modality compared with other endoscopic treatment modalities. However, at least two studies have shown that epinephrine injection plus APC is as efficient as epinephrine injection plus heater probe for bleeding peptic ulcers.(6, 7)

It is also important to mention that 4 of 5 of our rebleeding episodes were effectively controlled by combined endoscopic therapy; as compared with Javid *et al.* study that each rebleeding episode was treated by conservative therapy with or without surgery.(4), Only one of our patients who re-bleeded after two therapeutic endoscopy was referred for surgery.

The beneficial effect of PPIs in the setting of bleeding peptic ulcers may be due to their ability to maintain a gastric pH at a level above 6.0, and thus enhances platelet aggregation and protect an ulcer clot from fibrinolysis.(8), Additionally, at this level of gastric PH, proteolytic activity of pepsin is reduced.

CONCLUSION

In conclusion, it is evident that although combined endoscopic treatment with Argon Plasma Coagulator and epinephrine injection is highly efficient, probably more efficient than endoscopic injection therapy, addition of high dose omeprazole to endoscopic therapy is accompanied with statistically significant reduction of rebleeding rate in patients with bleeding peptic ulcer and we recommend routine inclusion of high dose oral omeprazole in the therapeutic regimen of these patients.

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