American Journal of Gastroenterology
ISSN 0002-9270

doi: 10.1111/j.1572-0241.2006.00399.x
Published by Blackwell Publishing

Role of Intravenous Omeprazole in Patients with High-Risk Peptic Ulcer Bleeding After Successful Endoscopic Epinephrine Injection: A Prospective Randomized Comparative Trial

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BACKGROUND: Epinephrine injection is the most common endoscopic therapy for peptic ulcer bleeding. Controversy exists concerning the optimal dose of proton pump inhibitors (PPI) for patients with bleeding peptic ulcers after successful endoscopic therapy. The objective of this study was to determine the optimal dose of PPI after successful endoscopic epinephrine injection in patients with bleeding peptic ulcers.

METHODS: A total of 200 peptic ulcer patients with active bleeding or nonbleeding visible vessels (NBVV) who had obtained initial hemostasis with endoscopic injection of epinephrine were randomized to receive omeprazole 40 mg infusion every 6 h, omeprazole 40 mg infusion every 12 h or cimetidine (CIM) 400 mg infusion every 12 h. Outcomes were checked at 14 days after enrollment.

RESULTS: Rebleeding episodes were fewer in the group with omeprazole 40 mg infusion every 6 h (6/67, 9%) as compared with that of the CIM infusion group (22/67, 32.8%, $p < 0.01$). The volume of blood transfusion was less in the group with omeprazole 40 mg every 6 h than in those groups with omepraole 40 mg infusion every 12 h ($p = 0.001$) and CIM 400 mg infusion every 12 h ($p < 0.001$). The hospital stay, number of patients requiring urgent operation, and death rate were not statistically different among the three groups.

CONCLUSION: A combination of endoscopic epinephrine injection and a large dose of omeprazole infusion is superior to combined endoscopic epinephrine injection with CIM infusion for preventing recurrent bleeding from peptic ulcers with active bleeding or NBVV.

(Am J Gastroenterol 2006;101:500–505)

INTRODUCTION

A bleeding peptic ulcer remains a serious medical problem with significant morbidity and mortality. Endoscopic therapy significantly reduces further bleeding, surgery, and mortality in patients with bleeding peptic ulcers and is now recommended as the first hemostatic modality for these patients (1, 2).

Epinephrine injection alone or in combination with another technique has become the most popular endoscopic therapy for peptic ulcer bleeding because of its safety, low cost, and ease of application (3). Whether epinephrine injection in combination with a second hematostatic therapy is better than epinephrine injection alone remains controversial (4–6).

Although a high initial hemostatic rate can be obtained with endoscopic injection of epinephrine, rebleeding occurs in 10–36% of these patients (3, 7, 8). In previous studies, patients received H-2 receptor-antagonists (H2RAs) intravenously after successful endoscopic hemostasis. In this way, intragastric pH could not be maintained higher than 4.0 for a long period in such patients (9–12). Therefore, their rebleeding rates were higher than expected.

Pharmacologically, omeprazole can quickly achieve an optimal intragastric pH condition for support of the physiological cascade of hemostasis (13). The optimal dose has been determined as continuous infusion of 8 mg/h or 160 mg/day of omeprazole (13–15). If we used a proton pump inhibitor (PPI) instead of H2RAs following endoscopic therapy, would it be possible to prevent further bleeding in high-risk patients?

So far, there have been several points of controversy concerning high-dose PPI, *e.g.*, cost-effectiveness, ideal dosage, and whether such a regimen should be reserved for high-risk patients (6). Large dose of IV PPI has been found to

be effective in reducing rebleeding after successful endoscopic therapy (16–19). In contrast, there have been other reports of regular IV doses, regular or higher oral doses of PPI that could reduce the rebleeding rate as well (20–23). So far, the evidence of the efficacy of IV PPI after endosocpic epinephrine injection is still scarce. Therefore, it would be interesting to investigate the role and optimal dose of PPI in high-risk bleeding ulcer patients after successful endoscopic injection with epinephrine.

The objective of this study is to assess the optimal dose of IV omeprazole *versus* cimetidine (CIM) in patients with bleeding peptic ulcers after initial hemostasis has been achieved with endoscopic injection of epinephrine.

METHODS

Patients were accepted for endoscopic therapy if a peptic ulcer with active bleeding or a nonbleeding visible vessel (NBVV) was observed within 12 h of hospital admission. The possibility of endoscopic therapy was discussed with patients and/or their relatives and a written informed consent was obtained before the trial. After initial hemostasis was achieved with endoscopic injection of diluted epinephrine, the patients were enrolled in this study. The study was approved by the Clinical Research Committee of the Veterans General Hospital, Taipei, Taiwan.

Patients were excluded from the study if they were pregnant, did not obtain initial hemostasis with endoscopic injection of epinephrine, did not give written informed consent, had bleeding tendency (platelet count $<50 \times 10^9$/L, serum prothrombin <30% of normal, or were taking anticoagulants), uremia, or bleeding gastric cancer.

For enrolled patients, an Olympus GIF-XQ240 end-view endoscope and an NM-8L injector were used to perform endoscopic injection. Epinephrine 1:10,000, 0.5–1.0 mL aliquots was injected around the bleeder or NBVV. In general, approximately 8–20 mL of diluted epinephrine was injected for each bleeder.

Patients enrolled in the study were randomly allocated into three groups using sealed envelopes containing a therapeutic option (CIM, omeprazole 40 mg q12 h and omeprazole 40 mg q6 h) derived from a randomized table. In the CIM group, we gave 400 mg continuous infusion every 12 h for 3 days. Thereafter, 400 mg of CIM was given orally twice daily for 2 months. In the omeprazole 40 mg q12 h (OME40q12h) group, we gave 40 mg omeprazole (AstraZeneca, Molndal, Sweden) continuous infusion every 12 h for 3 days. Thereafter, 20 mg omeprazole was given orally once daily for 2 months. In the omeprazole 40 mg q6 h (OME40q6h) group, we gave 40 mg continuous infusion every 6 h for 3 days. Thereafter, 20 mg omeprazole was given orally once daily for 2 months. Endoscopy was undertaken 72 h after enrollment. If no blood clot or hemorrhage was observed at the ulcer base, the patient was discharged and followed up in the outpatient department.

Patients' vital signs were checked every hour for the first 12 h, every 2 h for the second 12 h, and every 4 h for the following 24 h until they stabilized, then four times daily. The hemoglobin level and hematocrit were checked at least once daily, and a blood transfusion was given if the hemoglobin level decreased to lower than 90 g/L or if the patient's vital signs deteriorated. The attending physicians or surgeons were made aware of the exact endoscopic findings and treatment given in each case.

Active bleeding was defined as a continuous blood flow spurting or oozing from the ulcer base. An NBVV at endoscopy was defined as a discrete protuberance at the ulcer base that was resistant to washing and was often associated with the freshest clot in the ulcer base. Shock was defined as systolic blood pressure lower than 100 mmHg and a pulse rate of more than 100/min accompanied by cold sweats, pallor, and oliguria. Initial hemostasis was defined as no visible hemorrhage lasting for 5 min after endoscopic therapy. Ultimate hemostasis was defined as no rebleeding during the 14 days following endoscopic therapy.

Rebleeding was suspected upon unstable vital signs, continuous tarry, bloody stools, or a drop in the hemoglobin level of more than 20 g/L within 24 h was observed during hospitalization. For these patients, an emergency endoscopy was performed immediately. Rebleeding was determined if a fresh blood clot or bleeding in the ulcer base was found after endoscopic therapy. All patients with rebleeding were treated with heater probe thermocoagulation (HPT) unless they refused.

For the HPT, we used an Olympus GIF-XQ240 endoscope or an Olympus GIF-2T10 endoscope, an Olympus heater probe unit (Olympus Optical, Tokyo, Japan) and a 2.4 or 3.2 mm probe. During therapy, the distal tip of the heater probe was applied directly to the bleeding site. Initially, four to five pulses of 30 J/pulse were given. Afterwards, we withdrew the probe slowly. If rebleeding occurred, we repeated the above procedure until the bleeding stopped. Thereafter, we gave several pulses of 15–20 J/pulse in the area surrounding the bleeding site. The bleeding site was observed for 5 min. It was then challenged with maximal water irrigation for 10 s. If any further bleeding occurred, we started the initial procedure again as above. An emergency operation was performed if bleeding could not be controlled with HPT or if rebleeding occurred after two attempts with HPT therapy.

At entry to the study, the following data were recorded: age, sex, the location of the ulcer (esophagus, stomach, and duodenum), ulcer size, the appearance of the gastric contents (clear, coffee ground, and blood), endoscopic findings (spurting, oozing, and NBVV), number of shock, hemoglobin, number of patients with nonsteroidal anti-inflammatory drugs ingestion, number of positive rapid urease test, and comorbid illness.

The primary end points were recurrent bleeding before discharge and within 14 days. At day 14, volume of blood transfused, number of surgeries performed, and the mortality rates of the three groups were compared as well. Patients who had positive urease tests received a 1-wk course of omeprazole (20 mg twice daily), clarithromycin (500 mg twice daily), and amoxicillin (1 g twice daily) after discharge.

The sample size estimation was based on an expected rebleeding rate of 30% in the CIM group (8). The trial was designed to detect a 25% difference in favor of the omeprazole group with a type I error of 0.05 and type II error of 0.2. At least 43 patients were required for each group.

One way analysis of variance was used to compare age, volume of blood transfusion, volume of injected epinephrine, ulcer size, hemoglobin, and length of hospital stay.

The χ^2 test, with or without Yates's correction, and Fisher's exact test were used when appropriate to compare the location of bleeders, endoscopic findings, gastric contents, number of patients with *Helicobacter pylori* infection, number of patients with NSAID ingestion, number in shock, number with comorbid illness, hemostasis, emergency operation, and mortality among three groups. A p value of less than 0.05 was considered significant.

RESULTS

Between January 2003 and January 2005, 1,721 patients whose main symptoms were hematemesis, tarry stool, or both, visited the emergency room. A total of 1,520 patients received an emergency endoscopic examination within 12 h of arrival at the emergency department. A total of 1,380 patients had peptic ulcers. Patients with active bleeding or NBVV were found in 214 patients (Fig. 1). Fourteen patients were excluded from the study for the following reasons: lack of informed consent (n = 2), bleeding tendency (n = 3), lack of cooperation (n = 2), gastric malignancy (n = 3), and inability to obtain initial hemostasis with endoscopic injection of epinephrine (n = 4). In total, there were 200 patients enrolled in this study (66 patients in the OME40q12h group, 67 patients in the OME40q6h group, and 67 patients in the CIM group). The three groups were well matched for the factors affecting outcome (Table 1).

Table 2 shows the clinical outcome of the studied patients. We injected a similar dose of epinephrine among three groups. Rebleeding occurred in 14 (21.2%) patients in the OME40q12h group (7 patients within 24 h, four on the 2nd day, and three on the 3rd day), 6 (9%) patients in the OME40q6h group (5 patients within 24 h, 1 on the 2nd day), and 22 (32.8%) patients in the CIM group (18 patients within 24 h, 2 on the 2nd day, one on the 3rd day, and 1 on the 7th day). The rebleeding rate of the OME40q6h group was lower than that of the CIM group ($p = 0.0014$, risk ratio = 0.27, 95% CI: 0.12–0.63).

During routine follow-up endoscopic examination on the 3rd day, ulcers with clean bases were found in 42 patients (OMEq12h), 50 patients (OMEq6h), and 40 patients (CIM); ulcers with pigmented spots were found in 10 patients (OMEq12h), 11 patients (OMEq6h), and 6 patients (CIM), respectively.

Rebleeding occurred in 14 patients (21.2%) in the OME40q12h group. Of these patients, 11 patients received heater probe therapy and recovered uneventfully; 1 patient received embolization and recovered uneventfully; 1 patient received injection of epinephrine plus pure ethanol (he died of sepsis and continuous bleeding thereafter); 1 patient refused

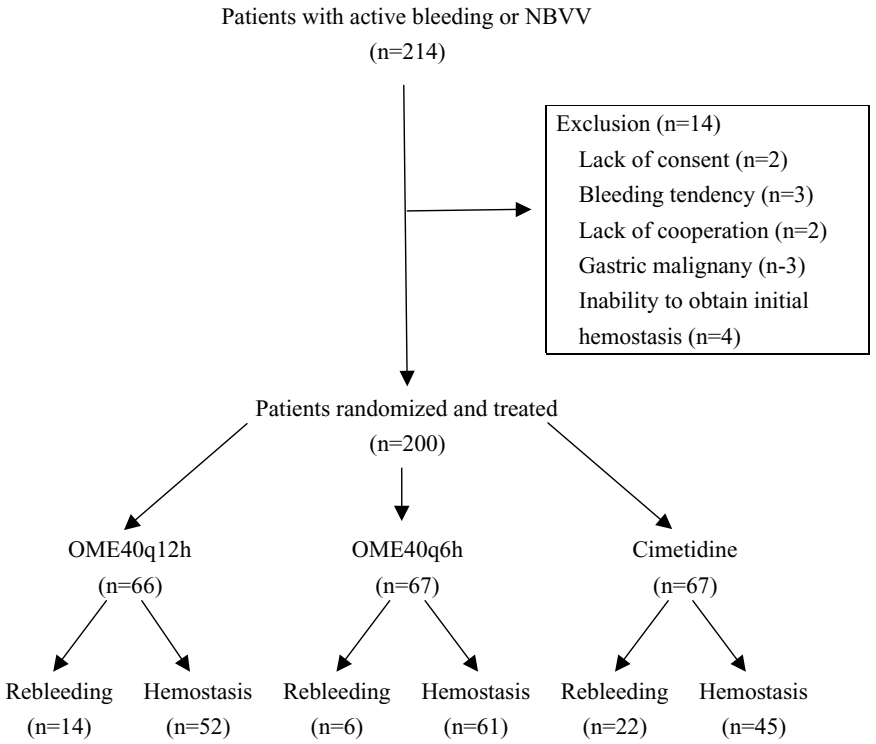

Figure 1. Test profile. Patients with active bleeding or NBVV.

Table 1. Clinical Variables of Patients at Entry to the Study

	OME40q6h (n = 67)	OME40q12h (n = 66)	CIM (n = 67)
Age (mean, yr)	67	71	68
Sex (M/F)	58/9	57/9	61/6
Location of bleeders			
Stomach	26	29	32
Duodenum	35	33	32
Esophagus	6	4	3
Endoscopic findings			
Spurting	3	3	5
Oozing	40	32	41
NBVV	5	13	10
Clot	18	17	11
Gastric contents			
Blood	18	24	24
Coffee grounds	25	20	22
Clear	24	22	21
Number in shock	32	21	25
Number with medical illness	53	50	44
Mean ulcer size (cm)	0.98	1.11	0.96
Number of positive urease test	45	43	43
Number with NSAID ingestion	18	16	20
Mean hemoglobin (g/L)	9.84	9.32	9.41
Mean body weight (kg)	65.1	64.2	64.6

No statistical difference among three groups.

further management and died thereafter. Rebleeding occurred in 6 patients in the OME40q6h group. They received heater probe therapy and recovered uneventfully.

Rebleeding occurred in 22 patients in the CIM group. Of these patients, 14 patients received heater probe therapy and recovered uneventfully; 2 patients received injection of epinephrine plus pure ethanol and recovered uneventfully; 3 patients refused further endosocpic therapy due to underlying malignancy and died thereafter; 3 patients received operation and recovered smoothly.

The volume of blood transfusion was lower in the OME40q6h group than in those of the OME40q12h group ($p = 0.001$) and the CIM group ($p < 0.001$). There were fewer surgical interventions and number of deaths in the OME40q6h group and OME40q12h group as compared with those in the CIM group, but the difference was not statistically significant. The duration of hospital stay was not statistically different among the three groups.

No patient had perforation, aspiration pneumonia, or fever within 1 wk following endoscopic therapy in any group.

DISCUSSION

The use of PPI after obtaining successful endoscopic therapy has been supported in many studies. In a consensus meeting for clinical guidelines, an IV bolus followed by continuous infusion of PPI was recommended in bleeding peptic ulcer patients who had undergone successful endoscopic therapy (16). In a recent meta-analysis, Andriulli *et al.* found that combination of endotherapy with PPI was beneficial for patients with bleeding peptic ulcers (20). In a meta-analysis of 11 randomized comparative trials, Gisbert *et al.* found that PPI was more effective than H2RAs in preventing recurrent bleeding and reducing the need for surgery (24). However, there may be several limitations in these studies. For example, the dose and route of PPI administration along with the modality of endoscopic therapy were different among various studies. In this study, we tried to evaluate the role of omeprazole with a unified dose and route following endoscopic injection of epinephrine in bleeding ulcer patients.

Patients with major bleeding and endoscopic evidence of an ulcer with active bleeding or a NBVV are at high risk for persistent or recurrent bleeding and should receive endoscopic therapy (2). Our prospective randomized trial was designed to ascertain whether IV large dose of omeprazole therapy after initial endoscopic hemostasis might further reduce the rebleeding rate in such patients.

Endoscopic injection with diluted epinephrine is easy to apply and is widely used throughout the world. This is the main reason that we decided to choose epinephrine injection as the therapeutic modality in this study. Unfortunately, the rebleeding rate following epinephrine injection was not negligible. In our previous observation, the rebleeding rates following epinephrine injection were 16–36% (8, 25). In one large meta-analysis series, the rebleeding rate was 18.8% (108/575) (6). After obtaining initial hemostasis, rebleeding is the most important prognostic factor. If the rebleeding rate can be lowered with IV PPI, endoscopic injection with epinephrine will be the most ideal modality for endoscopic therapy. In our previous observations, rebleeding episodes occurred within

Table 2. Results of Patients Receiving Endoscopic Treatment

	OME40q6h (n = 67)	OME40q12h (n = 66)	CIM (n = 67)	*p* Value
Volume of injected epinephrine (mL)	9.64 (8.74-10.54)	9.83 (8.62–10.96)	9.30 (8.59–10.32)	0.67
Volume of blood transfusion after therapy (mL)	710 (489–913)	1,241 (487–1,995)	1,317 (947–1,660)*	<0.01
Number achieving initial hemostasis	67	66	67	1
Number of rebleeding	6	14	22**	<0.01
Number receiving heater probe	6	11	14	0.15
Number of surgeries	0	0	3	0.12
Hospital stay (days)	5.89 (4.69–7.09)	7.64 (6.42–8.85)	7.92 (6.52–9.33)	0.21
Number of deaths	0	1	3	0.17

For volume of injected epinephrine, blood transfusion, and hospital stay, data are expressed as mean (95% CI).
*$p = 0.001$ between OME40q6h group and OME 40q12h group; $p < 0.001$ between OME 40q6h group and CIM group.
**$p < 0.01$ between OME40q6h and CIM groups.

3 days following endoscopic therapy in most instances (26–28). Therefore, we gave high-dose omeprazole in the first 3 days following endoscopic therapy.

In this study, we found that patients receiving omeprazole 40 mg IV infusion every 6 h after successful initial hemostasis had a lower rebleeding rate (6/67 *vs* 22/67, $p < 0.01$) and a lower volume of blood transfusion (mean 710 mL *vs* 1,317 mL, $p < 0.001$) as compared with patients who received CIM 400 mg every 12 h intravenously.

Hsu *et al.* recently conducted a similar study (29). They enrolled peptic ulcer patients with active bleeding or major signs of recent bleeding. They gave pantoprazole 40 mg IV bolus followed by 40 mg every 12 h for 3 days in one group, and ranitidine 50 mg intravenously every 8 h for 3 days in another group after endoscopic injection of distilled water. The rebleeding rate was lower in the pantoprazole group (2/52 *vs* 8/50, $p = 0.04$) when compared with that of the ranitidine group.

How about the role of oral PPIs in these patients? Khuroo *et al.* demonstrated that the recurrent bleeding rate was reduced to 11.8% in patients with visible vessels who received oral omeprazole 40 mg twice daily for 5 days (30). Javid *et al.* gave oral omeprazole 40 mg every 12 h for 5 days as compared with placebo in patients with high-risk peptic ulcer bleeding after endoscopic injection of epinephrine plus 1% polidocanol (23). They found that oral omeprazole is effective in reducing hospital stay, rebleeding rate, and the need for blood transfusion. Kaviani *et al.* conducted a similar study which favored oral omeprazole in high-risk patients in reducing the rebleeding rate after endoscopic injection (22). In a meta-analysis, Andriulli *et al.* also found that oral PPI reduced the rebleeding rate and the need for surgery (20). Unfortunately, there was no data showing intragastric pH in these studies.

In our study, we did not give oral PPI to the studied patients because intragastric pH exceeds 4.0 only after frequent high dosages (31, 32). Since rebleeding episodes occur within 24 h in the majority of patients (26), if we gave oral PPI to the patients, the rebleeding may have occurred before high intragastric pH was achieved. An intragastric pH higher than 6.0 is a prerequisite for preventing rebleeding in patients with bleeding peptic ulcers (33). Therefore, a drug that rapidly increases intragastric pH and lasts for 3–4 days is necessary to prevent rebleeding. Under such conditions, IV PPI is the drug of choice.

How about the effects of PPI dosage on rebleeding? In a randomized, double-blind study, Udd *et al.* found that regular-dose and high-dose omeprazole are both effective in preventing rebleeding after endoscopic therapy in bleeding peptic ulcer patients (21). However, intragastric pH cannot be elevated within a short period of time with the use of regular dose of PPI. In this way, rebleeding may occur. In addition, they included 38 patients with a low-risk rebleeding rate (Forrest IIc, ulcers with a black base). Such patients with low-risk endoscopic stigmata are not indicated for endoscopic hemostatic therapy (16). In addition, the endoscopic therapies are different among studied cases. Subsequently, there may be some bias in this study. In our study, higher dosage of PPI (160 mg/day) was more beneficial than lower dosage of PPI (80 mg/day) in decreasing the volume of blood transfusion. There was a lower rebleeding tendency for the OMEq6h group as compared with that of the OMEq12h group (6/67 *vs* 14/66, $p = 0.083$). It may have clinical significance showing that a bigger dose of PPI is favored in high-risk patients.

There may be one limitation in this study. Endoscopic therapy with epinephrine injection may be suboptimal. In our previous study, we used HPT or multipolar electrocoagulation to treat the patients and obtained a lower rebleeding rate (18). Under this situation, a smaller sample size may be enough to show statistically significant difference.

CONCLUSION

Large dose of IV PPI reduces the rebleeding rate in high-risk patients with bleeding peptic ulcers who have obtained initial hemostasis with epinephrine injection.

ACKNOWLEDGMENT

We are indebted to Ms. Betty Tzu-en Lin and Alex Jen-hao Lin for assistance of this study.

STUDY HIGHLIGHTS

What is Current Knowledge

- Endoscopic injection of epinephrine is a standard hemostatic modality for bleeding peptic ulcer.
- The optimal dose of proton pump inhibitor to prescribe post hemostatic therapy is unclear.

What is New Here

- A randomized controlled trial tested whether an infusion of emeprazole (40mg 6 or 12 hourly) or cimetidine (400mg 12 hourly) prevented rebleeding in high risk patients (active bleeding or non-bleeding visible vessels successfully treated with epinephrine injection endoscopically).
- Rebleeding occurred in 22/67 on cimetidine compared with 14/66 on omeprazole 40mg 12 hourly and 6/67 on omeprazole 40mg 6 hourly.
- After initial hemostasis, high dose intravenous proton pump inhibitor therapy is superior to intravenous H2 receptor antagonist therapy.

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Received July 15, 2005; accepted September 28, 2005.

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