Seven-day intravenous low-dose omeprazole infusion reduces peptic ulcer rebleeding for patients with comorbidities CME

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Background: Patients with comorbidities have an increased risk of ulcer rebleeding, especially within the 28 days after endoscopic therapy. Omeprazole infusion can prevent rebleeding after endoscopic therapy in patients with peptic ulcer bleeding. However, the optimal duration is uncertain, especially for those patients with comorbidities.

Objective: To determine whether prolonged low-dose intravenous omeprazole could reduce rebleeding for patients with comorbidities.

Design: A prospective randomized control study.

Setting: National Cheng Kung University, Tainan, Taiwan.

Patients: A total of 147 patients with comorbidities and peptic ulcer bleeding controlled by endoscopic hemostasis were enrolled.

Interventions: The enrolled patients were randomized into either the 7-day low-dose group or the 3-day high-dose group, who received 3.3 mg/h or 8 mg/h continuous omeprazole infusion, respectively. After omeprazole infusion, oral esomeprazole 40 mg every day was given.

Main Outcome Measurements: To compare the rebleeding rates within 28 days after gastroscopy between the 2 study groups.

Results: The 7-day cumulative rebleeding rate was similar between the 2 groups (9.5% vs 9.7%, $P > .05$), but the 7-day low-dose group had a lower risk of rebleeding between the 8th and 28th day compared with the 3-day high-dose group (0% vs 10.7%, $P = .03$; relative risk, 0.52 [95% CI, 0.43-0.63]). The Kaplan-Meier curves confirmed that the 7-day low-dose group had a significantly higher cumulative rebleeding-free proportion between the 8th and 28th day than the 3-day high-dose group ($P = .02$, log-rank test).

Conclusions: In Asian patients, prolonged low-dose omeprazole infusion for 7 days may reduce peptic ulcer rebleeding during the first 28 days in patients with comorbidities. (Gastrointest Endosc 2009;70:433-9.)

Peptic ulcer bleeding is a common and potentially lethal condition. Rebleeding is an independent risk factor of mortality,[1] with risks that have been positively linked with the presence of comorbidities.[2,3] The mortality in patients with comorbidities and bleeding can be caused not only by the rebleeding itself but also by the exacerbation of the comorbidities after bleeding or repetitive rebleeding.[2-7] In contrast to those patients without comorbidities, our previous study illustrated that patients with comorbidities could experience recurrent bleeding from peptic ulcers as late as 4 to 14 days after the initial bleeding episode.[3,7]

Irrespective to the continuous infusion of omeprazole with either a low dose (3.3 mg/h) or a high dose (8 mg/h) within the first 3 days after endoscopy, the cumulative peptic ulcer rebleeding still remained high, at nearly

Abbreviations: aPTT, activated partial thromboplastin time; ASA, American Society of Anesthesiologists; Hb, hemoglobin; ICU, intensive care unit; IV, intravenous; SRH, stigmata of recent hemorrhage.

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30% during the 4th to 28th day.[7] Hence, this study aimed to determine whether a longer course of intravenous (IV) omeprazole infusion, which is more effective in maintaining favorable intragastric pH, could effectively reduce ulcer rebleeding in patients with comorbidities.

IV proton pump infusion was confirmed with a positive impact on the prevention of rebleeding peptic ulcer in patients who are receiving endoscopic local therapy.[8-11] Perhaps because of the small parietal mass or higher prevalence of a poor metabolizer of cytochrome P450 CYP2C19 allele in the oriental population,[12,13] a decreased dosage of omeprazole infusion, to 3.3 mg/h, could effectively maintain a favorable intragastric pH in a country such as Taiwan.[7,10] Because the dosage of the 3-day high-dose omeprazole infusion could be reduced from 8 mg/h to 3.3 mg/h, this study shifted the 3-day high-dose medication to a 7-day low-dose medication with the same drug cost of omeprazole infusion.

In this study, we introduced a favorable approach, with a prolonged low-dose omeprazole infusion, to obtain near zero rebleeding during the 8th to 28th day after the first bleeding episode. These data show the originality and clinical importance of a prolonged duration of omeprazole infusion for such high-risk patients with comorbidities with peptic ulcer bleeding.

Capsule Summary

What is already known on this topic

- Within 28 days after endoscopic therapy, patients with peptic ulcers and comorbidities have an increased risk of rebleeding, which may, in turn, exacerbate the comorbidities.

What this study adds to our knowledge

- In 147 patients with comorbidities and peptic ulcer bleeding that was controlled by endoscopic hemostasis, a 7-day course of IV low-dose omeprazole infusion achieved better control of delayed rebleeding than did the 3-day high-dose regimen of the drug.

PATIENTS AND METHODS

Patients

From April 2004 to April 2008, a total of 147 patients with one or more comorbidities, who were undergoing upper gastroscopy because of peptic ulcer bleeding with stigmata of recent hemorrhage (SRH), and proven to have good hemostasis by endoscopic therapy, were consecutively enrolled in this study. The SRH was defined as either major or minor in our previous report.[14] All of the major SRHs were treated by either local injection of diluted epinephrine 1:10,000, with or without combined therapy with heat probe, argon plasma coagulation, band ligation, or hemoclip therapy to eradicate the vessel.

The spectra of the comorbidities included chronic obstructive pulmonary disease, pneumonia, restrictive lung disease, end-stage renal disease that required hemodialysis, chronic kidney disease or acute renal failure, congestive heart failure, coronary artery disease, liver cirrhosis, disseminated malignancy status, and new-onset cerebrovascular accident.

All of the enrolled patients were >60 years old and, on enrollment, had been assessed by using the American Society of Anesthesiologists (ASA) classification[15] and the Rockall risk scoring system after gastroscopy.[1] Patients were excluded if they had tumor bleeding, ulcer bleeding because of mechanical factors (eg, induction of gastrostomy tube), warfarin usage, or even failure to establish hemostasis by endoscopic local therapy.

Study design and treatment protocols

This study design was approved by the hospital's ethics committee. After obtaining informed consent, each enrolled patient received an 80 mg bolus injection of IV omeprazole (Losec; AstraZeneca AB, Södertälje, Sweden) immediately after hemostasis by using endoscopic therapy. In addition, if the patients had a spurting artery, active oozing, or nonbleeding visible vessel lesions, a heat probe, hemoclip, argon plasma coagulation, band ligation of vessels, or combination therapy was used to eradicate the vessel if possible.

Each patient was then randomized by chart code into either the low-dose group (7-day continuous omeprazole infusion at 3.3 mg/h) or the high-dose group (3-day continuous omeprazole infusion at 8 mg/h). Patients with *Helicobacter pylori* infection, defined either by a positive rapid urease test (CLO test; Kimberly-Clark, Draper, Utah) or histology, were treated with a 7-day course of triple therapy that included 500 mg clarithromycin, 1 g amoxicillin, and 40 mg esomeprazole twice daily after cessation of the omeprazole infusion. After omeprazole infusion (some after 7-day triple therapy for *H. pylori* eradication), oral esomeprazole (Nexium; AstraZeneca AB) 40 mg every day was given until the end of follow-up. All of the enrolled patients were included in the intention-to-treat analysis, but patients who were lost to follow-up or died from their comorbidities were excluded from the per-protocol analysis.

Outcome measures

All of the patients were followed-up as possible, until 28 days after panendoscopy; the primary end point was rebleeding within this period. Documented rebleeding should fulfill one of the following conditions: (1) continuous melena, hematochezia, or the presence of recurrent bloody aspirates through the nasogastric tube, or (2) relapse of hemodynamic instability, including systolic blood pressure <90 mm Hg, heart rate >120 beats/min, or a hemoglobin (Hb) level drop of more than 2 g/dL.

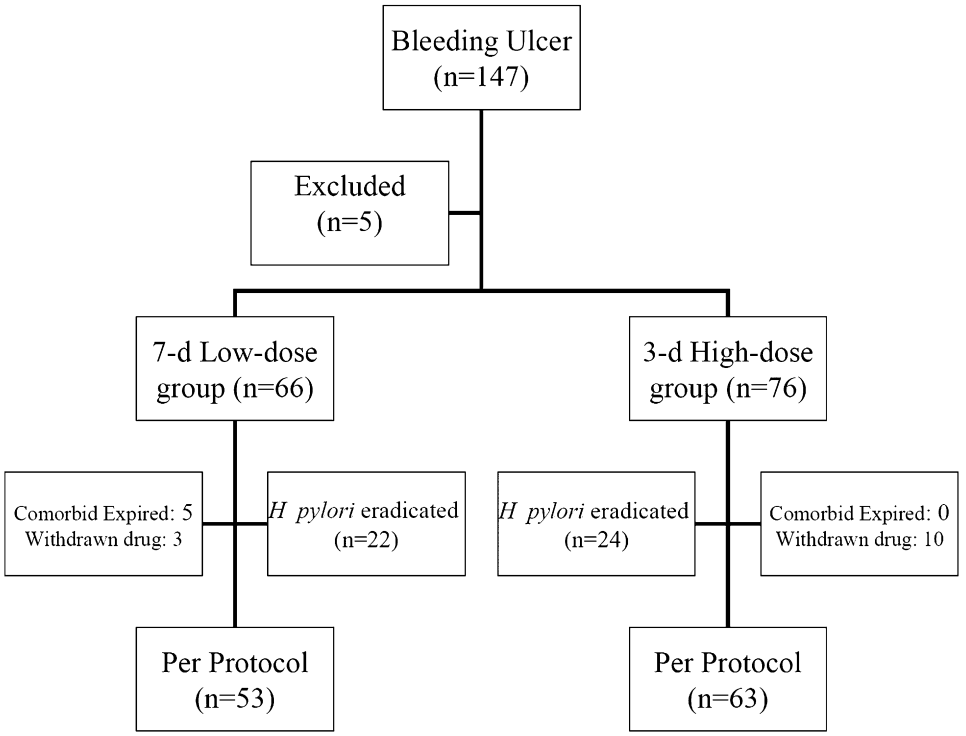

Figure 1. The schematic flow chart, showing the study design and patient numbers during follow-up.

For each patient with either suspected or active rebleeding, panendoscopy was conducted to confirm any blood or coffee-ground materials in the stomach, or the persistence of SRH. The panendoscopy also determined if the rebleeding source was a peptic ulcer or other nonulcer bleeding sources, such as varices.

Statistical analysis

The Student *t* test, Fisher exact test, and Pearson χ^2 test were used to determine the parametric difference and nonparametric proportions between the 2 study groups. The Kaplan-Meier curve was used to compare the differences of the cumulative proportions of the patients free from rebleeding between the 2 groups by using the log-rank test. The Fisher exact test determined the relative risk with 95% CI of the 7-day low-dose group to have rebleeding during the different time periods compared with the 3-day high-dose group. Also, multiple logistic regressions were applied to detect the independent risk factors related to rebleeding during the different follow-up periods. All tests of significance were 2 tailed, with a P value $<.05$. To achieve a study power of 90% ($\beta = 0.10$), our sample size should be at least 88 subjects.

RESULTS

Demographic background of the treatment groups

This study consecutively enrolled 147 patients with peptic ulcer bleeding and successful hemostasis by therapeutic gastroscopy. Five patients were excluded: 2 with gastric cancer bleeding, 1 with pancreatic cancer with duodenal invasion, and 2 with variceal bleeding. The remaining 142 patients were randomized by the chart code into either the 7-day low-dose group (n = 66) or the 3-day high-dose group (n = 76). As shown in Figure 1, 8 patients in the 7-day low-dose group (5 died from comorbidities but not from bleeding, and 3 had discontinued esomeprazole) and 10 patients in the 3-day high-dose group (all had discontinued esomeprazole) were defined as protocol violation and were excluded from the per-protocol analysis. All of the patients excluded from per-protocol analysis had no rebleeding episodes up to 28th day and thus were included in the intention-to-treat analysis for the rebleeding rate. There were similar protocol violations during the follow-up period between the 2 groups ($P > .05$).

Three patients died because of the recurrence of rebleeding in each group. In the 7-day low-dose group, the comorbidities of the 3 cases with uncontrolled bleeding were hepatoma rupture, metastatic adenocarcinoma with grade 4 performance of Eastern Cooperative Oncology Group performance status scale, and end-stage renal disease. In the 3-day low-dose group, the comorbidities of the 3 cases with uncontrolled bleeding were bilateral transitional-cell carcinoma, pneumonia with impending respiratory failure, and Pugh C liver cirrhosis with untreated hepatoma. Because of the poor prognosis of these patients, none were referred to surgery, and they died of recurrent bleeding.

On enrollment, the demographic background, ulcer characteristics, and clinical features possibly related with rebleeding were not significantly different between the

TABLE 1. Baseline characteristics of the 2 study groups

Parameters	7-Day low-dose group (n = 66)	3-Day high-dose group (n = 76)	*P* value*
Women:men	23:43	26:50	.94
Mean age (y)	71.3	69.3	.34
Ulcer characteristics (n)			
Stomach:duodenum:both	38:24:4	40:32:4	.79
Major SRH:minor SRH	64:2	74:2	.99
Mean ulcer size (cm)	1.4	1.2	.27
Gastroscopic therapy (n)			
Nil:epinephrine alone:combination therapies	6:23:37	4:32:40	.68
H pylori infection (%)	43.1	42.9	.98
NSAID user (%)	23.1	13.2	.12
ASA physical status classification (n)			
Class II:III:IV:V	4:41:19:2	8:42:23:3	.75
Rockall risk score (n)			
Score <6:≥ 6	7:59	8:68	.99
Bleeding to shock (%)	18.2	19.7	.81
Mean Hb (g/dL)‡	9.0	9.0	.91
Platelet $<80{,}000/mm^3$ (%)‡	12.1	10.5	.76
PT prolong ≥ 4 s (%)‡	4.6	2.7	.67
aPTT prolong ≥ 1.5-fold (%)‡	3.1	9.6	.17
Serum albumin <3 g/dL (%)‡	54.7	41.5	.14
Creatinine ≥ 1.5 mg/dL (%)‡	50.0	57.9	.35

Major SRH, Spurting vessel, nonbleeding visible vessel, or fresh adherent clot; *Minor SRH,* old adherent clot or cherry red spot; *NSAID,* nonsteroidal anti-inflammatory drugs; *PT,* prothrombin time; *aPTT*, activated partial thromboplastin time.
*Student *t* test, Fisher exact test, and Pearson χ^2 test were used as appropriate.
‡Reference ranges: Hb level, 13.5-17 g/dL; platelet count, 138.1-353.4 $\times$ $10^3/mm^3$; albumin level, 3-5 g/dL; creatinine, 0.7-1.5 mg/dL.

2 groups (Table 1). The endoscopic treatment modalities were performed by 5 expert endoscopists, and the selection of treatment modalities were likewise similar between the 2 study groups ($P = .5$). There were 6 patients in the 7-day low-dose group (9.1%) and 4 patients in the 3-day high-dose group (5.3%) who had no endoscopic therapy because they had either minor SRH or blood clots without visible vessel.

Also shown in Table 1, the majority of patients enrolled in both the groups were class III and IV by the ASA classification (low-dose group vs high-dose group: 90.9% vs 85.5%, $P > .05$) and had similarly high proportions of the Rockall risk score ≥ 6 (low-dose group vs high-dose group: 89.4% vs 89.5%, respectively; $P > .05$). In Figure 2, there was no difference in the distribution of comorbidities, intensive care unit (ICU) stay, and mechanical ventilation between the 2 study groups ($P > .05$).

The second-look endoscopy was routinely suggested on the third day of the infusion for both groups. However, only 38 patients in the 7-day low-dose group (57.6%) and 39 patients in the 3-day high-dose group (51.3%) received the second-look endoscopy. Most of the study patients who received the second-look endoscopy achieved fading of SRH. Only 6 patients in the 7-day low-dose group (15.8%) and 7 patients in the 3-day high-dose group (17.9%) still had SRH and had received similar endoscopic modality by epinephrine injection plus heat probe.

Different duration of omeprazole infusion and rebleeding rates

In Table 2, the 7-day cumulative rebleeding rate was similar between the 7-day low-dose and the 3-day high-dose groups (per protocol 9.5% [6/63] vs 9.7% [7/72], respectively; $P > .05$; intention to treat: 9.1% [6/66] vs 9.2% [7/76], respectively; $P > .05$). The Kaplan-Meier curves (Fig. 3) showed similar cumulative rebleeding proportions within the 7-day follow-up between the 2 study groups ($P = .93$, log-rank test). However, between the 8th and 28th day, there were significantly lower rebleeding rates in the 7-day low-dose group than in the 3-day high-dose group based on per-protocol analysis (0% [0/46] vs 10.7% [6/56]; $P = .03$; relative risk: 0.52 [95% CI, 0.43-0.63]). Moreover, the Kaplan-Meier curves (Fig. 4) showed the proportion of patients free from rebleeding during the 8th to 28th day was significantly higher in the 7-day low-dose group than in the 3-day high-dose group ($P = .02$, log-rank test).

Factors related to rebleeding after omeprazole infusion

In Table 3, the significant univariate factors related to rebleeding within the first 7 days included the presence of malignancy, prolonged activated partial thromboplastin time (aPTT) ≥ 1.5-fold, and serum albumin level <3 g/dL (normal 3–5 g/dL) ($P < .05$). The multiple logistic regressions confirmed that patients with malignancy and serum albumin level <3 g/dL were 2 independent risk factors. Only the 3-day high-dose group had recurrent bleeding during the 8th to 28th day. There was no significant independent risk factor related to determine the rebleeding in such patients during the 8th to 28th day on follow-up.

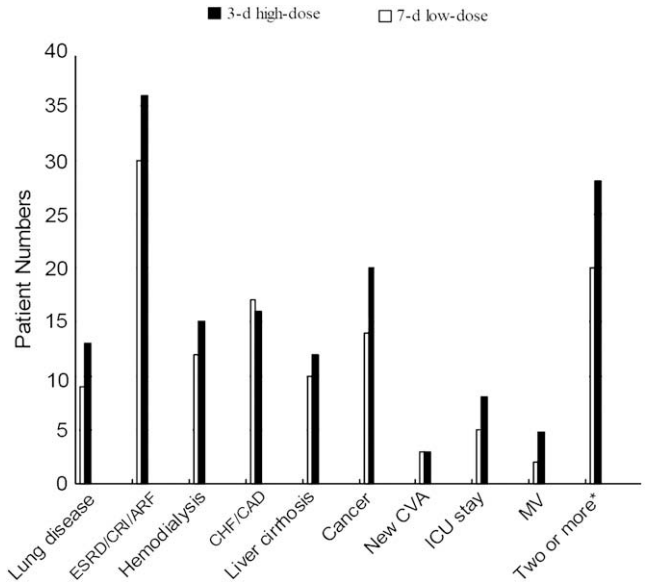

Figure 2. The patient numbers of the underlying comorbidities of the 2 study groups. *MV,* mechanical ventilation applied for such patients. *Patient numbers with more than 2 comorbidities.

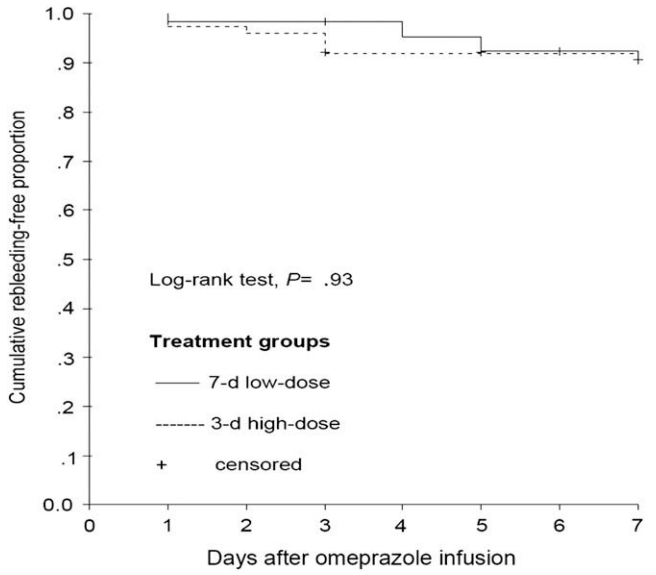

Figure 3. The Kaplan-Meier curves estimated that the cumulative rebleeding-free proportion within 7 days after omeprazole infusion were not significantly different between the 2 study groups ($P > .05$, log-rank test).

TABLE 2. Cumulative rebleeding rates by ITT and PP analysis

Rebleeding rate %(n)	7-Day low-dose group	3-Day high-dose group	*P* value*	Relative risk (95% CI)
7-d (ITT)	9.1 (6/66)	9.2 (7/76)	.98	0.99 (0.59-1.69)
7-d (PP)	9.5 (6/63)	9.7 (7/72)	.97	0.99 (0.58-1.68)
8th-28th d (ITT)	0 (0/57)	9.5 (6/63)	.03	0.50 (0.42-0.60)
8th-28th d (PP)	0 (0/46)	10.7 (6/56)	.03	0.52 (0.43-0.63)

ITT, Intention to treat; *PP,* per protocol.
*The Fisher exact test was used with 2-tailed analysis.

DISCUSSION

There are various factors recognized as possibly related to peptic ulcer rebleeding, including age, *H pylori* status, nonsteroidal anti-inflammatory drug use, the presence of shock, 2 or more comorbidities, a low serum albumin level, endoscopic features with major stigmata of hemorrhages, and even different therapeutic approaches.[3,6,7,16-19] Two groups with similar conditions of physical status classified by the ASA and the Rockall risk score (Table 1, $P > .05$) were randomized. As shown in Table 1 and Figure 2, there are no differences in the possible confounding factors between the 2 study groups. Moreover, there are similar endoscopic hemostasis approaches between the 2 groups. Hence, the trial should have corrected the potential hazards, which may interfere with the rebleeding outcomes.

Our study is the first intervention trial on the prolonged low-dose omeprazole infusion (3.3 mg/h up to 7 days) for patients with a bleeding peptic ulcer and comorbidities. This study design was for enrollment of a regular control group to receive the traditionally suggested 3-day course of high-dose omeprazole infusion (8 mg/h). Our results disclose similar rates of 7-day rebleeding between the 2 groups, either by per-protocol or intention-to-treat analysis (Table 3). This suggests that there will be no additional benefits by the prolongation of omeprazole infusion for the first 7 days after endoscopic injection therapy, even in patients with high comorbidities.

Notably, the delayed rebleeding rate between the 8th to 28th day is significantly lower in the 7-day low-dose group than in the 3-day high-dose group (0% vs 10.7%, respectively; $P = .03$; relative risk 0.52). Moreover, the Kaplan-Meier curve confirms that there should be significantly higher proportions of patients free from rebleeding during this period in the 7-day low-dose group than in the 3-day high-dose group ($P = .03$, log-rank test) (Fig. 4). These data support the idea that, among patients with comorbidities, the 7-day course of IV low-dose omeprazole infusion has better control of delayed rebleeding between the 8th to 28th day. However, further studies are needed in Western populations, among whom a larger parietal cell mass may be present, to confirm the efficacy of low-dose omeprazole infusion to reduce the incidence of recurrent hemorrhage.

The reason why prolonged omeprazole infusion up to 7 days has favorable control of rebleeding since 8th until 28th day is uncertain. We propose that the prolonged

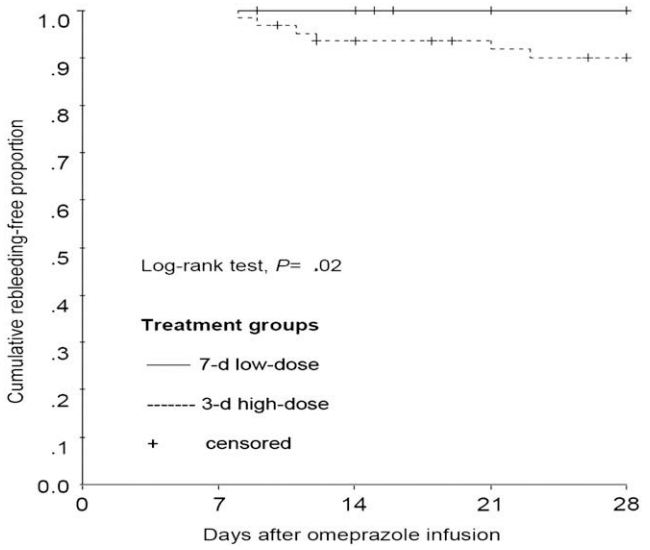

Figure 4. The Kaplan-Meier curves estimated that the cumulative rebleeding-free proportion from the 8th to 28th day after omeprazole infusion was significantly higher in the 7-day low-dose group than in the 3-day high-dose group ($P = .02$, log rank test).

course might offer better gastric-acid control than the oral form only. It may enhance the resolution of the vascular cuff, which usually persists longer in patients with comorbidities than in the general population.[7] Serial 24-hour pH monitoring for acid suppression by prolonged omeprazole infusion during different time periods in patients with bleeding ulcers should be promising to answer this question. Accordingly, further studies that investigate gastric-acid secretion rates with oral versus low-dose omeprazole infusions may be needed to understand whether there is better acid control with the low-dose infusion than with an oral proton pump inhibitor.

Although the treatment course was longer, patients in the 7-day low-dose group did not use more IV omeprazole than those in the 3-day high-dose group (640 vs 656 mg, respectively). The cost of omeprazole infusion, therefore, was not increased. Nevertheless, the cost of prolonged admission up to 7 days remained debatable. In our study, most of our enrolled patients (nearly 90%) had a high Rockall risk scoring system >6, which indicated that the mean hospital stay after acute upper-GI hemorrhage should be more than 10 days.[8] Thus, the total cost of admission for giving 7-day omeprazole infusion was not significantly increased in such patients with comorbidities.

In contrast, there is a need to consider how to decrease rebleeding during these periods for an earlier hospital discharge. Our data show that prolonged low-dose omeprazole infusion is not only cost beneficial but also can reduce delayed rebleeding in such patients with comorbidities, and, especially for those patients with high Rockall risk scores (>6), their additional costs for admission can be avoided. In Table 3, we show that a low serum albumin level of <3 g/dL (17.2% vs 4.7%; odds ratio 4.24, $P = .025$) and

TABLE 3. Significant univariate analysis and multivariate logistic regression to determine factors associated with rebleeding in the different study periods

Related factors on different periods	Rebleeding rates (%)	Odd ratio (95% CI)	P value
Univariate analysis			
Within 7 d			
Cancer vs noncancer	23.3 vs 5.7	5.02 (1.54-16.36)	.009*
aPTT prolong ≥1.5-fold vs <1.5-fold	33.3 vs 8.1	5.65 (1.22-26.08)	.045*
Serum albumin <3 g/dL vs ≥3 g/dL	17.2 vs 4.7	4.24 (1.10-16.25)	.025*
During 8th-28th d in the 3-d high-dose group			
Ventilator used vs none	40.0 vs 7.8	7.83 (0.99-61.46)	.084*
Multivariate logistic regression			
Within 7 d			
Cancer vs noncancer		3.56 (1.01-12.60)	.049†
aPTT prolong ≥1.5-fold vs <1.5-fold		4.67 (0.82-26.45)	.082†
Serum albumin <3 g/dL vs ≥3 g/dL		4.58 (1.10-19.16)	.037†

aPTT, Activated partial thromboplastin time.
*Assessed by a 2-tailed Fisher exact test.
†Indicates the significance of the multivariate logistic regression. Because the 7-d low-dose group had no rebleeding from the 8th to 28th day, the data show the univariate factor borderline related with the rebleeding in the 3-d high-dose group.

comorbidity with disseminated cancer (23.3% vs 5.7%; odds ratio 5.02, $P = .009$) were 2 independent factors in having a higher risk of peptic ulcer rebleeding within 7 days in patients with comorbidities, either in the 7-day low-dose group or in the 3-day high-dose group. These data are compatible to show that patients with disseminated cancer status have more rebleeding and higher mortality after peptic ulcer bleeding.[1]

However, there are still limited studies that focus on the exact causal relationship of low serum albumin concentration to higher rebleeding. We supposed that serum albumin should be an important parameter in assessing the nutritional status of patients who are acutely ill and those who are chronically ill. Therefore, it may be a malnutrition indicator to associate with poor wound healing.[20] The meta-

analysis by Vincent et al[21] showed that the complication rates of patients who are acutely ill may be reduced when the serum albumin level attained during albumin administration exceeds 3.0 g/dL. The exact mechanism of albumin and its effect on decreasing ulcer rebleeding in patients with comorbidities require further investigation.

Despite the common demands of the comorbidity to have prolonged admission near 7 days or more, it remains of concern to test whether the prolonged low-dose omeprazole infusion can be shifted to oral form early during admission. Laine et al[22] presented an important finding that showed that frequent oral proton-pump inhibitor may replace the currently recommended IV infusion of proton-pump inhibitor therapy in patients with bleeding ulcers, although the IV therapies may be superior to the oral forms. Further study is thus necessary to resolve this concern. In summary, in Asian patients with comorbidities, delayed rebleeding risk of peptic ulcer after endoscopic hemostasis may be significantly reduced by a prolonged course of low-dose omeprazole infusion up to 7 days.

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