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Efficacy of an intravenous proton pump inhibitor after endoscopic therapy with epinephrine injection for peptic ulcer bleeding in patients with uraemia: a case–control study

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SUMMARY

Background
Patients with peptic ulcer bleeding and uraemia are prone to re-bleeding.

Aim
To compare the efficacy of an intravenous proton pump inhibitor in treating peptic ulcer bleeding in patients with uraemia and those without uraemia.

Methods
High-risk peptic ulcer bleeding patients received endoscopic therapy with epinephrine (adrenaline) injection plus intravenous omeprazole (40 mg bolus followed by 40 mg infusion every 12 h) for 3 days. Re-bleeding, volume of blood transfusion, hospital stay, need for surgery, and mortality were analysed.

Results
The uraemic group had similar 7-day re-bleeding rate (6/42, 14.29% vs. 6/46, 13.04%, $P = 0.865$) to that of non-uraemic patients, but more re-bleeding episodes beyond 7 days (4/42, 9.52% vs. 0/46, 0%, $P = 0.032$, OR [95% CI] = 1.105 [1.002–1.219]) and all-cause mortality (4/42 vs. 0/46 $P = 0.032$, OR [95% CI] = 1.105 [1.002–1.219]). The uraemic group also had more units of blood transfusion after endoscopic therapy (mean ± s.d. 4.33 ± 3.35 units vs. 2.15 ± 1.65 units, $P < 0.001$), longer hospital stay (mean ± s.d. 8.55 ± 8.12 days vs. 4.11 ± 1.60 days, $P < 0.001$) and complications during hospitalization (9/42 vs. 0/46, $P = 0.001$, OR [95% CI] = 1.273 [1.087–1.490]).

Conclusion
Endoscopic therapy with epinephrine injection plus an intravenous proton pump inhibitor can offer protection against early re-bleeding in uraemic patients with peptic ulcer bleeding, but has a limited role beyond 7 days.

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INTRODUCTION

Peptic ulcer bleeding (PUB) remains a serious medical problem with significant morbidity and mortality.[1] Endoscopic therapy significantly reduces further bleeding, the need for surgery and mortality in PUB patients.[2] The addition of a proton pump inhibitor (PPI) after successful initial endoscopic haemostasis has been proven beneficial in such patients.[3–7] Therefore, it is recommended that endoscopic therapy followed by intravenous (adrenaline) PPI therapy be the mainstay of current treatment for high-risk PUB.[1]

However, re-bleeding is frequently encountered in PUB patients with co-morbidities, especially uraemia, despite the aforementioned management.[8, 9] The efficacy of endoscopic therapy and intravenous PPI in uraemic patients with PUB remains unclear.

This study aimed to compare the efficacies of endoscopic therapy with epinephrine injection and intravenous PPI on the clinical outcomes of high-risk PUB patients with and without uraemia.

MATERIALS AND METHODS

Uraemic patients receiving regular haemodialysis (uraemic symptoms plus serum creatinine >10 mg/dL for more than 3 months before dialysis) and non-uraemic patients (age- and gender-matched patients with normal renal function) with gastric or duodenal ulcer bleeding and high-risk stigmata [spurting or oozing haemorrhage, non-bleeding visible vessel (NBVV) and adherent blood clot] were accepted for endoscopic therapy within 12 h of hospital admission. Written informed consent was obtained from the patients and/or their relatives before the study.

Two experienced gastroenterologists (Tseng GY and Lin HJ) performed all of the endoscopic therapies using an endoscope (GIF-XQ240, Olympus Optical Co., Ltd., Tokyo, Japan) and an NM-8L injector for endoscopic injection. Epinephrine, 1:10000, 0.5–1 mL aliquots was injected around the bleeder or NBVV until the bleeding stopped. In general, approximately 8–20 mL of diluted epinephrine was injected for each bleeder. Initial haemostasis was defined as no visible haemorrhage lasting for 5 min after endoscopic therapy. After successful initial haemostasis, the patients were enrolled in this study.

The patients subsequently received omeprazole (AstraZeneca, Molndal, Sweden) 40 mg intravenous bolus followed by 40 mg every 12 h continuous infusion for 3 days. Thereafter, 20 mg omeprazole was given orally once daily for 2 months. Patients who had a positive urease test or a positive pathology examination (haematoxylin and eosin stain, and modified Giemsa stain) received a 1-week course of omeprazole (20 mg twice daily), clarithromycin (500 mg twice daily) and amoxicillin (1 g twice daily) after discharge.

The 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. Haemoglobin level was checked at least once daily and a blood transfusion was given if the haemoglobin was <9 g/dL or if the patient's vital signs deteriorated. Re-bleeding was suspected when there were unstable vital signs, continuous tarry or bloody stools or a drop in the haemoglobin level >2 g/dL within 24 h. Emergency endoscopy was immediately done for these patients. Re-bleeding was confirmed by fresh blood clot or bleeding in the ulcer base found after endoscopic therapy. All patients with re-bleeding were treated with heater probe thermocoagulation (HPT) unless they refused.

In patients without re-bleeding, follow-up endoscopy was performed 72 h after enrollment. If there was no blood clot or haemorrhage at the ulcer base, the patient was discharged and followed-up in the outpatient department for 30 days. During this period, the uraemic group received regular haemodialysis without using coagulants (e.g. heparin).

The sample size was calculated according to a previous study. The re-bleeding rates in PUB patients with and without co-morbid illnesses were 37.5% and 5% respectively.[8] It was assumed that the re-bleeding rate of patients with uraemia was similar to those with co-morbid illnesses. A sample size of 30 was thus required for each group (uraemic and non-uraemic) to achieve a statistical power of 80% at 10% type I error. The Ethics Committee of the Ton-Yen General Hospital, Hsin-Chu, and Lotung Poh-Ai Hospital, Yi-Lan in Taiwan approved this study.

Patients with cardio-vascular disease (CVD), chronic obstructive pulmonary disease (COPD), liver cirrhosis, bleeding tendency (low platelet count $<100 \times 10^3$/u, serum prothrombin <30% of normal, or on coumadin), malignancy, prior gastric surgery, pregnancy or lactating, receiving anti-ulcer therapy (e.g. H_2-receptor antagonists, sucralfate, proton pump inhibitors, bismuth salt or antibiotics) within the past 7 days were excluded. Also excluded were those with drug allergy or

Zollinger–Ellison syndrome and those with inability to provide informed consent or to co-operate.

An ulcer was defined as a circumscribed mucosal break (>5 mm in diameter, with apparent depth) in the stomach or duodenum, covered with exudates. Active bleeding was defined as continuous blood flow spurting or oozing from the ulcer base. An NBVV on endoscopy was defined as a discrete protuberance at the ulcer base that was resistant to washing and often associated with the freshest clot in the ulcer base. Patients with CVD were defined as having any of the following conditions: (i) typical chest pain with positive treadmill exercise test, (ii) significantly positive result of coronary arterial angiography, (iii) history of cerebro-vascular infarct or ischaemic heart disease and (iv) signs of peripheral occlusive artery disease.

Hypertension was defined as a systolic blood pressure >140 mmHg, diastolic pressure >90 mmHg or a prior history of hypertension that needed anti-hypertensive therapy. Diabetic mellitus (DM) was defined as fasting blood sugar >125 mg/dL on at least two occasions or a positive DM history that required hypoglycaemic therapy. Shock was defined as systolic blood pressure <100 mmHg and pulse rate >100 beats/min accompanied by cold sweats, pallor and oliguria. A positive history of non-steroidal anti-inflammatory drugs (NSAIDs) ingestion was defined as >1 tablet/day NSAIDs ingestion within 7 days of enrolment. Positive cigarette smoking was defined as ≥10 cigarettes per day for at least 1 year, while positive alcohol drinking was defined as ≥40 g/day alcohol consumption for at least 6 months.

The primary outcomes included re-bleeding episodes, while secondary outcomes were the need for surgery, all-cause mortality, units of blood transfusion after endoscopy, hospital stay and complications within 30 days.

Statistical analysis

All statistical tests were performed using the software SPSS, Chicago, IL, USA, for Windows, version 13.0. Student's *t* test and Mann–Whitney *U* test were used to analyse non-parametric quantitative data (i.e. age, ulcer size, ulcer number, haemodialysis duration, initial haemoglobin and units of blood transfusion). The chi-square test with or without Yates' correction and the odds ratio with 95% confidence interval (CI) were used, where appropriate, to compare the re-bleeding rate, need for surgery, all cause mortality and demographic data such as gender, hypertension, DM, ulcer location, stigmata of recent haemorrhage at the ulcer base and shock at initial presentation.

A multivariate logistic regression test was applied to detect independent risk factors related to re-bleeding during the follow-up period. A P value <0.05 was considered statistically significant.

RESULTS

Between January 2003 and December 2006, 642 patients with uraemia under maintenance haemodialysis were screened in this study. Among them, there were 102 upper gastro-intestinal (UGI) bleeding episodes and 54 cases were high-risk peptic ulcer bleeding (PUB) on endoscopy. A total of 106 uraemic and age- and gender-matched non-uraemic patients with high-risk PUB after initial endoscopic injection with diluted epinephrine were initially included in this study. After excluding 12 cases in the uraemic group (three liver cirrhosis, two COPD, five CVD, one prior gastrectomy and one malignancy) and six cases in the non-uraemic group (two liver cirrhosis and one each for COPD, CVD, prior gastrectomy and malignancy), 42 patients with uraemia and 46 patients without uraemia were enrolled (Figure 1).

Most clinical variables were comparable between the two groups. However, the uraemic group had more patients with DM and hypertension and lower haemoglobin level (haemoglobin <10 gm/dL) on initial presentation (Tables 1 and 2). Nonetheless, such diseases and/or conditions were usually related to uraemia *per se*. Following intravenous proton pump infusion, there were no adverse effects during the 30-day follow-up.

The uraemic and non-uraemic groups had similar three-day (3/42, 7.14% vs. 3/46, 6.52%, $P = 0.908$) and seven-day re-bleeding rate (6/42, 14.29% vs. 6/46, 13.04%, $P = 0.865$) (Table 3). However, there were more re-bleeding episodes beyond 7 days in the uraemic group than in the non-uraemic group (4/42, 9.52% vs. 0/46, 0%, $P = 0.032$, OR [95%CI] = 1.105 [1.002–1.219]) (Table 3). Among the patients with re-bleeding, nine (90%) in the uraemic group and six (100%) in the non-uraemic group achieved successful haemostasis by heat probe thermo-coagulation and all of them had uneventful courses thereafter.

One patient in the uraemic group received surgery for massive bleeding that could not be controlled by heat probe thermo-coagulation on the 3rd hospital

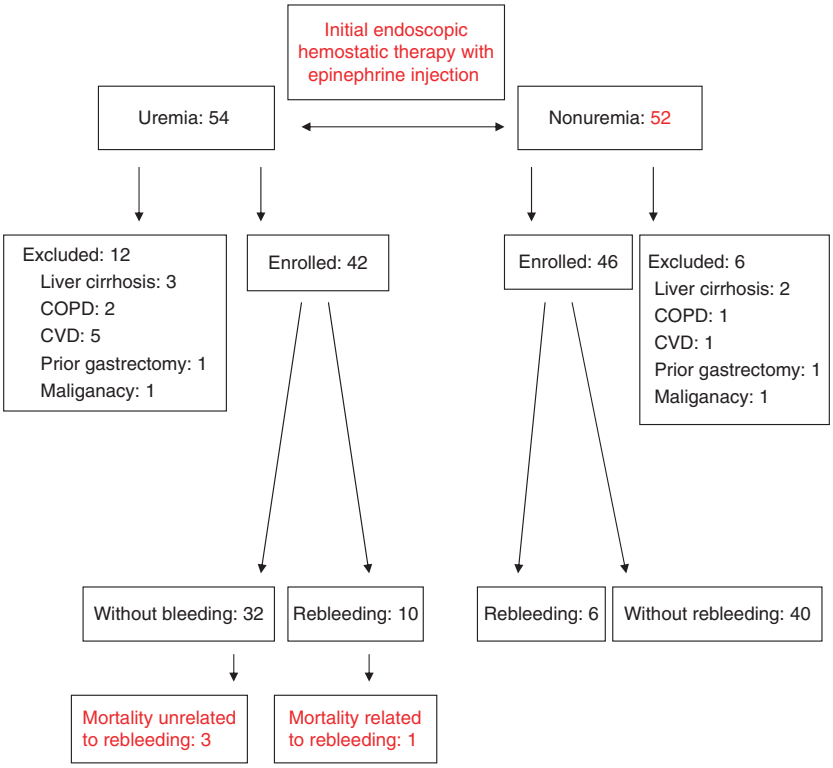

Figure 1. Study profile. EHT, endoscopic hemostatic therapy.

day. The patient died on the 5th hospital day because of multiple organ failure. All-cause mortality was significantly higher in the uraemic group during the 30-day follow-up (9.52%, 4/42 vs. 0%, 0/46, $P = 0.032$, OR [95%CI] = 1.105 [1.002–1.219]). In the uraemic group, two died of heart failure, one of sepsis and heart failure and the other of re-bleeding.

There were more complications during the hospitalization in the uraemic group than in the non-uraemic group (21.43%, 9/42 vs. 0%, 0/46, $P = 0.001$, OR [95%CI] = 1.273 [1.087–1.490]) (Table 3). The mean hospital stay was longer in the uraemic group (mean thinsp;± s.d. 8.55 ± 8.12 days vs. 4.11 ± 1.60 days, $P < 0.001$). More units of blood were transfused after endoscopy was more in the uraemic group than in the non-uraemic group (mean ± s.d. 4.33 ± 3.35 units vs. 2.15 ± 1.65 units, $P < 0.001$). There was a significantly positive correlation between the units of blood transfusion and the starting haemoglobin level in the study patients ($r = 0.224$, $P = 0.036$, Pearson correlation coefficient, two-tailed test).

Table 1. Demographic and clinical characteristics of the study patients

Patient no.	Patients with uraemia ($N = 42$)	Patients without uraemia ($N = 46$)	P value
Age, y/o (mean ± s.d.)	66.31 ± 12.91	65.52 ± 10.41	0.753
Gender (M/F)	24/18	25/21	0.792
Taking NSAID, no.	20	23	0.823
Hypertension, no.	28	14	0.001
DM, no.	17	9	0.032
H. pylori (+), no.	18	21	0.792
Low haemoglobin level (Hb <10 g/dL), no.	31	20	0.004
Initial Hb (g/dL, mean ± s.d.)	8.04 ± 2.20	10.56 ± 2.25	<0.001
Shock, no.	8	9	0.91

Table 2. Endoscopic features of the study patients

Patient no.	Patients with uraemia (N = 42)	Patients without uraemia (N = 46)	P value
Gastric content, no.			
Clear	21	26	0.540
Coffee ground	10	9	0.629
Blood	11	11	0.619
Index ulcer size, cm, mean ± s.d.	1.07 ± 0.66	0.95 ± 0.32	0.267
Ulcer location, no.			
Stomach/Duodenum	23/19	21/25	0.393
Stigmata of recent haemorrhage, no.			
Blood clot	12	11	0.459
NBVV	17	19	0.937
Oozing and spurting	13	16	0.703
Volume of injected epinephrine, mL (mean ± s.d.)	11.17 ± 4.08	10.283 ± 3.23	0.262

Table 3. Outcomes of bleeding patients included in the analyses

Patient no.	Patients with uraemia (N = 42)	Patients without uraemia (N = 46)	P value	Odds ratio (95% CI)
Units of blood transfused after endoscopy	4.33 ± 3.35	2.15 ± 1.65	<0.001	
Hospital stay, days				
Mean ± s.d.	8.55 ± 8.13	4.22 ± 1.83	0.001	
Re-bleeding, within 30 days				
Days ≤ 3	3 (7.14%)	3 (6.52%)	0.908	
Days ≤ 7	6 (14.29%)	6 (13.04%)	0.865	
Days ≤ 14	7 (16.67%)	6 (13.04%)	0.632	
Days ≤ 30	10 (23.81%)	6 (13.04%)	0.191	
7 < days ≤ 30	4 (9.52%)	0 (0%)	0.032	1.105 (1.002–1.219)
Need for surgery, no.	1	0	0.293	1.024 (0.979–1.074)
Complications during hospitalization, no.	9	0	0.001	1.273 (1.0875–1.490)
Infection	2	0		
Heart failure	5	0		
Infection & heart failure	1	0		
Multiple organ failure	1	0		
Mortality, all cause, no.	4	0	0.032	1.105 (1.002–1.219)
Mortality, bleeding related, no.	1	0	0.293	1.024 (0.979–1.074)

Multivariate logistic regression analysis was performed to determine the independent factors predictive of re-bleeding, mortality and complications occurring during hospitalization. Uraemia was the only significant predictor for re-bleeding after 7 days (P = 0.011). It was also the only significant factor associated with mortality (P = 0.046) and complications (P = 0.003).

DISCUSSION

The combination of endoscopic haemostatic therapy (EHT) and subsequent IV PPI treatment is supported by many studies.[1, 3–5, 7] In a meta-analysis of 24 randomized controlled trials, Leontiadis *et al.* reported that PPI treatment significantly reduces re-bleeding.[3] Moreover, it reduces mortality in Asian trials and

in patients with active bleeding or NBVV.[4] However, PUB patients with co-morbid illnesses are prone to re-bleeding despite IV PPI therapy.[8, 9] In a previous study, patients with uraemia are prone to peptic ulcer recurrence even after *Helicobacter pylori* eradication.[10] So far, there are no studies focusing on PUB patients with uraemia. It is therefore of great interest to evaluate the efficacy of endoscopic therapy followed by IV PPI in patients with uraemia as compared to those with normal renal function.

This study shows that IV PPI had a preventive effect against early (7-day) re-bleeding even in uraemic patients with high-risk PUB. The re-bleeding episodes are similar within 7 days (with IV PPI infusion) in both groups. Such finding implies that the initial pharmacological effects of IV PPI on PUB patients between those with and those without uraemia may be similar. In fact, a study measuring pharmacokinetics of rabeprazole in uraemic patients reports no difference between uraemic patients and normal controls.[11] Therefore, there is no need for dosage adjustment in dialysis patients using PPI.[11] Nonetheless, it is reported that IV PPI can prevent re-bleeding by raising intragastric pH.[5] Thus, gastric acidity may play a crucial role to be evaluated in determining the efficacy of PPI for PUB. However, gastric secretion in uraemic patients compared to normal controls remains controversial. Hyper-,[12] hypo-[13] and normal secretions have been reported.[14] Unfortunately, these studies have small sample sizes. There are studies that suggest the presence of heterogeneous subgroups in uraemic patients as regards acid secretion.[14] A recent report comparing intra-gastric pH between chronic renal failure (CRF) patients (19/27 were on haemodialysis) and normal control subjects found that chronic renal failure patients with *H. pylori* infection have a lower gastric acidity than those without *H. pylori* infection and normal controls, which results from neutralization of acid by ammonia and gastric atrophy.[15] Such effects of *H. pylori* infection on intra-gastric pH of uraemic patients may raise the concern of affecting re-bleeding. In a previous study, *H. pylori* could augment the effect of IV PPI in raising intra-gastric pH, whereas such was not associated with short-term re-bleeding in PUB.[16] Overall, although the result here shows that IV PPI is beneficial to PUB patients against early (7-day) re-bleeding both in uraemic patients and in normal controls, the effect of uraemia *per se* on intra-gastric pH in PUB patients using IV PPI still needs further investigation.

Such beneficial effect of IV PPI against re-bleeding is not shown in PUB patients with multiple co-morbidities.[8, 9] In one previous report, patients with multiple co-morbid illness receiving the same dose of IV PPI had higher re-bleeding rates than those without co-morbidities (7-day: 32.5% vs. 2.5%; 28-day: 37.5% vs. 5.0%).[8] Furthermore, patients with two or more co-morbidities have a higher risk of re-bleeding than those with single co-morbidity (66.7% vs. 26.5%).[8] Therefore, using IV PPI for PUB patients with multiple co-morbid illnesses does not prevent early (7-day) re-bleeding as it does for our studied patients, who have uraemia alone.

Patients with multiple co-morbidities may have a high possibility of re-bleeding. Considering that uraemic patients may also have multiple co-morbidities, the current study has excluded cases with co-morbid illnesses such as liver cirrhosis, CVD, COPD and bleeding tendency, which are all associated with peptic ulcer occurrence or re-bleeding in PUB patients. In addition, CVD is the single most important cause of death among patients with uraemia undergoing regular haemodialysis.[17, 18] Thus, they have to be excluded to avoid influencing short-term mortality. The 30-day re-bleeding rate of the uraemic patients here is 23.81%, which is similar to the 26.5% reported in patients with a single co-morbidity.[8]

Our finding also implies that 3-day IV PPI therapy has a limited role in preventing delayed (beyond 7 days) rebleeding for PUB patients with uraemia. Actually, the uraemic patients here have more delayed (beyond 7 days) re-bleeding episodes than the non-uraemic patients (9.52% vs. 0%, $P = 0.032$). Whether or not longer (more than 3 days) IV PPI use has a protective effect in patients with uraemia after 7 days warrants further study. However, the disease itself may explain the higher re-bleeding episodes beyond 7 days in uraemic patients. There is usually poor nutrition and low albumin in uraemic patients, thereby causing the ulcer to heal slowly.[9, 19] Vaziri *et al.* found significant ischaemic phenomena, including thrombosis, embolism and infarction involving the stomach and intestine in 78 autopsied uraemic patients.[20] In addition, uraemic patients tend to have platelet dysfunction and fibrinolysis.[21, 22] Therefore, poor nutritional status plus ischaemic change of the GI tract and bleeding tendency may result in re-bleeding.

The uraemic group tended to be more anaemic and therefore received higher volumes of blood transfu-

sions than the non-uraemic group. In this study, there is a significantly positive correlation between the units of blood transfusion and the starting haemoglobin level ($r = 0.224$, $P = 0.036$). Based on the results here, a lower starting haemoglobin level and more delayed re-bleeding cases can be two reasons for a higher volume of blood transfusions in uraemic groups.

The uraemic group also has more complications and all-cause mortality than those of the non-uraemic group. There were nine patients with complications during hospitalization in the uraemic group. Except for one patient who died of multiple organ failure after surgery for re-bleeding, the other eight were caused by heart failure and/or sepsis. Uraemia often results in immune deficiency.[23] ESRD patients are particularly susceptible to septicaemia and heart failure.[23, 24] There are possible explanations for infection and heart failure in uraemic patients. First, malnutrition is exacerbated by nothing *per os* after endoscopic therapy. Second, old age and uraemia *per se* may impair the immune system and result in infection.[23, 24] Third, low haemoglobin level may aggravate heart failure and infection.[25, 26] Fourth, left ventricular hypertrophy (LVH) is present in about three-quarters of patients starting dialysis, which is strongly linked to mortality.[27] Fifth, anaemia contributes to the development of LVH and increases the risk of arrhythmia, myocardial infarction and myocardial fibrosis.[26, 27] Furthermore, a haemoglobin level <11 g/dL is associated with increased morbidity and mortality.[25–27] Therefore, a more aggressive blood transfusion policy and earlier endoscopic haemostasis in uraemic PUB patients may prevent complications and mortality.

In this study, endoscopic injection with diluted epinephrine was used alone because it is easy to apply and is widely used.[7, 28] However, the re-bleeding rate following epinephrine injection is not negligible. In a previous observation, re-bleeding rates following epinephrine injection was 15–36%.[7, 28] The re-bleeding rate in non-uraemic patients here is 13%, which is comparable to the re-bleeding rate in a previous study.[7, 28] Therefore, it is important to use IV PPI subsequently to reduce the re-bleeding rate.[5, 28]

Instead of using high dose IV PPI, a dose of 40 mg every 12 h for 3 days was used in this study because of a study by Cheng *et al*.[9] They found that a daily dose of 80 or 200 mg PPI conferred a similar re-bleeding rate and intra-gastric pH (>6) in PUB patients with co-morbid illnesses, including uraemic patients. Moreover, PPI treatment in Asian patients may produce a more profound reduction in acid secretion because of a lower parietal cell mass, a higher prevalence of *H. pylori* infection and a higher proportion of slow PPI metabolizers.[29, 30]

This study has two limitations. First, the studied patients were not classified according to the Blactchford or Rockall scoring systems.[31, 32] These scoring systems usually regarded renal failure as a significant variable and there was no way to find matched cases without uraemia as controls. Uraemia *per se* should have some distinct characteristics of being prone to re-bleeding. Such factors on the outcomes of the therapies against PUB could be answered by multivariate logistic regression analysis. Second, the choice of endoscopic injection alone in this study is suboptimal for endoscopic therapy. Recent meta-analyses suggest that dual therapy is better than epinephrine injection alone in improving outcomes of patients with high-risk peptic ulcer bleeding.[33, 34] However, no consensus or guidelines were available during the conduct of this study. Therefore, further studies using dual endoscopic haemostasis are warranted.

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