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A STUDY ON ORAL OR INTRAVENOUS PROTON PUMP INHIBITOR IN PATIENTS WITH PEPTIC ULCER BLEEDING

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ABSTRACT

Peptic ulcer disease (PUD) is a break in the lining of the stomach, first part of the small intestine or occasionally the lower esophagus.[1][7] An ulcer in the stomach is known as a gastric ulcer while that in the first part of the intestines is known as a duodenal ulcer.[1] We aimed to assess the clinical effectiveness of oral *vs.* intravenous (i.v.) regular-dose proton pump inhibitor (PPI) after endoscopic injection of epinephrine in patients with peptic ulcer bleeding. Patients were excluded from the study if they were pregnant, did not obtain initial haemostasis with endoscopic injection of epinephrine, did not give written informed consent, had bleeding tendency (platelet count <50 × 10^9 l^{-1}, serum prothrombin<30% of normal, or were taking anticoagulants), had used PPI within 14 days of enrolment, had uraemia or bleeding gastric cancer. In summary, this single-centre, prospective, randomized, controlled trial of patients with high-risk bleeding ulcers has shown that oral and i.v. regular-dose PPI were equally effective as adjuvant pharmacotherapy to endoscopic haemostasis. Oral rabeprazole (20 mg twice daily) and i.v. infusion omeprazole (40 mg every 12 h) were not different in recurrent bleeding, surgery, blood transfusion or mortality. Our results suggest that oral PPI may be able to replace i.v. infusion PPI as the treatment of choice in peptic ulcer bleeding. However, more studies, particularly validating trials in Western countries, are necessary before oral PPI can be considered as the standard treatment.

INTRODUCTION

Peptic ulcer disease (**PUD**) is a break in the lining of the stomach, first part of the small intestine or occasionally the lower esophagus.[1][7] An ulcer in the stomach is known as

a **gastric ulcer** while that in the first part of the intestines is known as a **duodenal ulcer**.[1] The most common symptoms of a duodenal ulcer are waking at night with upper abdominal pain or upper abdominal pain that improves with eating.[1] With a gastric ulcer the pain may worsen with eating.[8] The pain is often described as a burning or dull ache.[1] Other symptoms include belching, vomiting, weight loss, or poor appetite.[1] About a third of older people have no symptoms.[1] Complications may include bleeding, perforation and blockage of the stomach.[2]Bleeding occurs in as many as 15% of people.[2]

Peptic ulcers are sores that develop in the lining of the stomach, lower esophagus, or small intestine. They're usually formed as a result of inflammation caused by the bacteria *H. pylori*, as well as from erosion from stomach acids. Peptic ulcers are a fairly common health problem.

There are three types of peptic ulcers.

- **gastric ulcers:** ulcers that develop inside the stomach
- **esophageal ulcers:** ulcers that develop inside the esophagus
- **duodenal ulcers:** ulcers that develop in the upper section of the small intestines, called the duodenum.

Common causes include the bacteria Helicobacter pylori and non-steroidal anti-inflammatory drugs (NSAIDs).[1] Other less common causes include tobacco smoking, stress due to serious illness, Behcet disease, Zollinger-Ellison syndrome, Crohn disease and liver cirrhosis, among others.[1][3] Older people are more sensitive to the ulcer-causing effects of NSAIDs.[1] The diagnosis is typically suspected due to the presenting symptoms with confirmation by either endoscopy or barium swallow.[1] *H. pylori* can be diagnosed by testing the blood for antibodies, a urea breath test, testing the stool for signs of the bacteria, or a biopsy of the stomach.[1] Other conditions that produce similar symptoms include stomach cancer, coronary heart disease, and inflammation of the stomach lining or gallbladder inflammation.[1]

Diet does not play an important role in either causing or preventing ulcers.[9] Treatment includes stopping smoking, stopping NSAIDs, stopping alcohol and giving medications to decrease stomach acid.[1] The medication used to decrease acid is usually either a proton pump inhibitor (PPI) or an H2 blocker with four weeks of treatment initially recommended.[1]Ulcers due to *H. pylori* are treated with a combination of medications such as amoxicillin, clarithromycin and a PPI.[4] Antibiotic resistance is increasing and thus

treatment may not always be effective.[4] Bleeding ulcers may be treated by endoscopy, with open surgery typically only used in cases in which it is not successful.[2]

Peptic ulcers are present in around 4% of the population.[1] New ulcers were found in around 87.4 million people worldwide during 2015.[5] About 10% of people develop a peptic ulcer at some point in their life.[10] They resulted in 267,500 deaths in 2015 down from 327,000 deaths in 1990.[6][11] The first description of a perforated peptic ulcer was in 1670 in Princess Henrietta of England.[2] *H. pylori* was first identified as causing peptic ulcers by Barry Marshall and Robin Warren in the late 20th century,[4] a discovery for which they received the Nobel Prize in 2005.[12]

Peptic ulcers are open sores that develop on the inside lining of your stomach and the upper portion of your small intestine. The most common symptom of a peptic ulcer is stomach pain. Peptic ulcers include.

- **Gastric ulcers** that occur on the inside of the stomach
- **Duodenal ulcers** that occur on the inside of the upper portion of your small intestine (duodenum)

The most common causes of peptic ulcers are infection with the bacterium Helicobacter pylori (H. pylori) and long-term use of aspirin and certain other painkillers, such as ibuprofen (Advil, Motrin, others) and naproxen sodium (Aleve, Anaprox, others). Stress and spicy foods do not cause peptic ulcers. However, they can make your symptoms worse.

SIGNS AND SYMPTOMS

The most common symptom of a peptic ulcer is burning abdominal pain that extends from the navel to the chest, which can range from mild to severe. In some cases, the pain may wake you up at night. Small peptic ulcers may not produce any symptoms in the early phases. Other common signs of a peptic ulcer include.

- changes in appetite
- nausea
- bloody or dark stools
- unexplained weight loss
- indigestion
- vomiting
- chest pain

- Burning stomach pain
- Feeling of fullness, bloating or belching
- Fatty food intolerance
- Heartburn
- Nausea

The most common peptic ulcer symptom is burning stomach pain. Stomach acid makes the pain worse, as does having an empty stomach. The pain can often be relieved by eating certain foods that buffer stomach acid or by taking an acid-reducing medication, but then it may come back. The pain may be worse between meals and at night.

We aimed to assess the clinical effectiveness of oral *vs.* intravenous (i.v.) regular-dose proton pump inhibitor (PPI) after endoscopic injection of epinephrine in patients with peptic ulcer bleeding. To assess the clinical effectiveness of oral *vs.* i.v. regular-dose PPI after endoscopic injection of epinephrine in patients with peptic ulcer bleeding.

MATERIALS AND METHODS

Design and patients

This was a single-centre prospective, randomized, controlled trial conducted in a tertiary teaching hospital (Veterans General Hospital, Taipei) in Taiwan and was approved by the Clinical Research Committee of the Veterans General Hospital, Taipei. From January 2007 to December 2007, peptic ulcer patients with high-risk stigmata were considered eligible if they fulfilled the following inclusion criteria: (i) underwent urgent endoscopy within 24 h after presentation, (ii) had peptic ulcers in the distal oesophagus, stomach or duodenum, (iii) had high-risk stigmata including active bleeding (Forrest IA, IB), nonbleeding visible vessels (NBVV, Forrest IIA), or adherent clots (Forrest IIB), and (iv) successful haemostasis was achieved with endoscopic injection of epinephrine. Written informed consent was obtained before enrolment.

Patients were excluded from the study if they were pregnant, did not obtain initial haemostasis with endoscopic injection of epinephrine, did not give written informed consent, had bleeding tendency (platelet count $<50 \times 10^9\ l^{-1}$, serum prothrombin<30% of normal, or were taking anticoagulants), had used PPI within 14 days of enrolment, had uraemia or bleeding gastric cancer.

Endoscopic procedures

For enrolled patients, an Olympus GIF-XQ240 video-endoscope and an NM-8L injector were used to perform the endoscopic injection. Active bleeding was defined as a continuous blood spurting (Forrest IA) or oozing (Forrest IB) from the ulcer base. An NBVV at endoscopy was defined as a discrete protuberance at the ulcer base (Forrest IIA). An adherent clot was resistant to forceful irrigation or suction (Forrest IIB). We injected 10 ml diluted epinephrine (at a 1: 10 000 ratio of epinephrine to saline) around the bleeder, NBVV or clot, and then observed the lesion for 3 min. If bleeding persisted, the patient was excluded from analysis and received other endoscopic therapies. All patients underwent endoscopic biopsy at gastric antrum for rapid urease test [Camplyobacter-like organism (CLO) test]. Those who were positive for urease test received a 1-week course of esomeprazole (40 mg twice daily) or rabeprazole (20 mg twice daily), plus clarithromycin (500 mg twice daily) and amoxicillin (1 g twice daily) after discharge.

Randomization process

Enrolled patients were randomly allocated into two groups using sealed envelopes containing a therapeutic option (either i.v. omeprazole or oral rabeprazole) derived from a random number table. In the omeprazole (OME) group, 40 mg continuous infusion of omeprazole was administered every 12 h for 3 days. Thereafter, the patients received oral esomeprazole 40 mg (Nexium®; AstraZeneca, Molndal, Sweden) once daily for 2 months. In the rabeprazole (RAB) group, we gave 20 mg of oral rabeprazole (Pariet®; Eisai Co., Ltd, Tokyo, Japan) twice daily for 3 days followed by once daily for 2 months. Endoscopy was repeated 72 h after enrolment. If no blood clot or haemorrhage was observed at the ulcer base, the patients were discharged and followed in the outpatient department.

Assessments

Patients' vital signs were checked every hour for the first 12 h, every 2 h for the second 12 h, every 4 h for the following 24 h until they became stable, and then four times daily. The haemoglobin level and haematocrit were checked at least once daily, and blood transfusion was given if the haemoglobin level decreased to lower than 90 g l^{-1} or if the patient's vital signs deteriorated. Shock was defined as systolic blood pressure <100 mmHg and a pulse rate of >100 min^{-1} accompanied by cold sweats, pallor or oligurea. Initial endoscopic haemostasis was defined as no visible haemorrhage with observation for 3 min. Ultimate haemostasis was defined as no rebleeding within 14 days after endoscopic therapy.

Rebleeding was suspected if unstable vital signs, continuous tarry, bloody stool, or a drop of haemoglobin level >20 g l^{-1} within 24 h were noted. For these patients, an emergent endoscopy was performed immediately. Rebleeding was concluded if active bleeding, fresh blood or blood clots were found. All patients with rebleeding were treated with rescue endoscopic therapies including heater probe thermocoagulation or haemoclip placement.

At entry to the study, the following data were recorded: age, sex, location of the ulcer (oesophagus, stomach, duodenum or stoma), ulcer size, appearance of the gastric contents (clear, coffee ground, or blood), bleeding stigmata (spurting, oozing or NBVV), volume of blood transfusion at entry, presence of shock, haemoglobin, nonsteroidal anti-inflammatory drug ingestion, cigarette smoking, alcohol drinking, and comorbid illness. The Rockall scoring system was used to assess the severity of bleeding in both groups.[25]

End-points

The primary end-point was 14-day rebleeding rate. Volume of blood transfusion, surgery, mortality within 14 days, and hospital stay were considered as secondary end-points.

Statistics

The sample size estimation was based on an expected rebleeding rate of 30% in the RAB group. The trial was designed to detect a 25% difference in favor of the OME group with a type I error of 0.05 and type II error of 0.05. At least 65 patients were essential for each group. Taking into account a possible drop-out rate of 15%, 78 patients were enrolled for each group in this study. We used unpaired Student's *t*-test to compare the numerical variables including age, ulcer size, volume of blood transfused, haemoglobin, and length of hospital stay between the two groups. Pearson's χ^2 test and Fisher's exact test were used (if expected frequency in any of the cells was <10) to compare categorical variables such as the location of the bleeders, endoscopic findings, gastric contents, number of patients with *Helicobacter pylori* infection, shock, comorbid illness, haemostasis, emergent surgery, and mortality between the two groups. All statistic examinations were two-tailed and a probability value of <0.05 was considered significant.

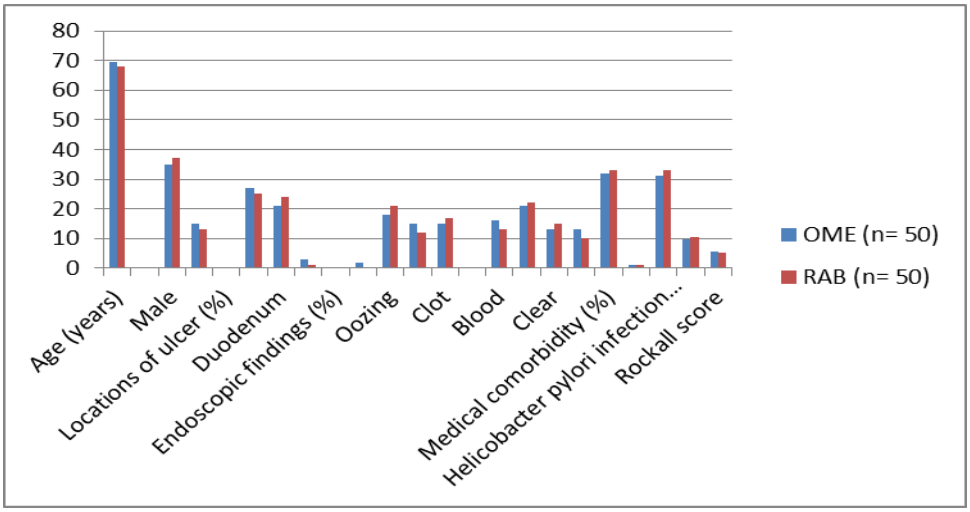
RESULTS AND DISCUSSION

Between and December 2017 to March 2018, 150 patients presented with haematemesis, tarry stool or both to the emergency room. A total of 130 patients received an urgent endoscopic examination within 24 h of arrival. Of the 130 patients with peptic ulcers, 100

had high-risk stigmata of active bleeding, NBVV, or adherent clot. Thirty patients were excluded from the study for the following reasons: lack of informed consent (*n*= 3), bleeding tendency (*n*= 3), lack of cooperation (*n*= 2), gastric malignancy (*n*= 3), prior use of PPI (*n*= 11) and failure to obtain initial haemostasis (*n*= 2) (Figure 1). Finally, 100 patients were enrolled in this study (50 in the OME group and 50 in the RAB group). The two groups were well matched for the factors affecting outcome (Table 1).

Table 1: Clinical variables of patients at entry to the study.

	OME (*n*= 50)	**RAB (*n*= 50)**
Age (years)	69.4 (20.3, 80.4)	67.9 (21.2, 81.9)
Sex (%)		
Male	35 (70.5%)	37(74.4%)
Female	15(29.5%)	13(25.6%)
Locations of ulcer (%)		
Stomach	27(53.8%)	25(50%)
Duodenum	21(41.0%)	24(47.4%)
Oesophagus	3(5.2%)	1(2.6%)
Endoscopic findings (%)		
Spurting	2(3.8%)	0
Oozing	18(35.9%)	21(42.3%)
NBVV	15(30.8%)	12(23.1%)
Clot	15(29.5%)	17(33.3%)
Gastric contents (%)		
Blood	16(32.1%)	13(25.6%)
Coffee grounds	21(42.3%)	22(44.9%)
Clear	13(25.6%)	15(29.5%)
Shock (%)	13(26.9%)	10(20.5%)
Medical comorbidity (%)	32(64.1%)	33(65.4%)
Ulcer size (cm)	1.06 (0.4, 2.0)	1.12 (0.5, 2.1)
Helicobacter pylori infection (%)	31(61.5%)	33(65.4%)
Haemoglobin (g l^{-1})	9.81 (9.32, 10.48)	10.31 (9.83, 10.85)
Rockall score	5.4 (3.8, 7.0)	5.3 (3.5, 7.1)

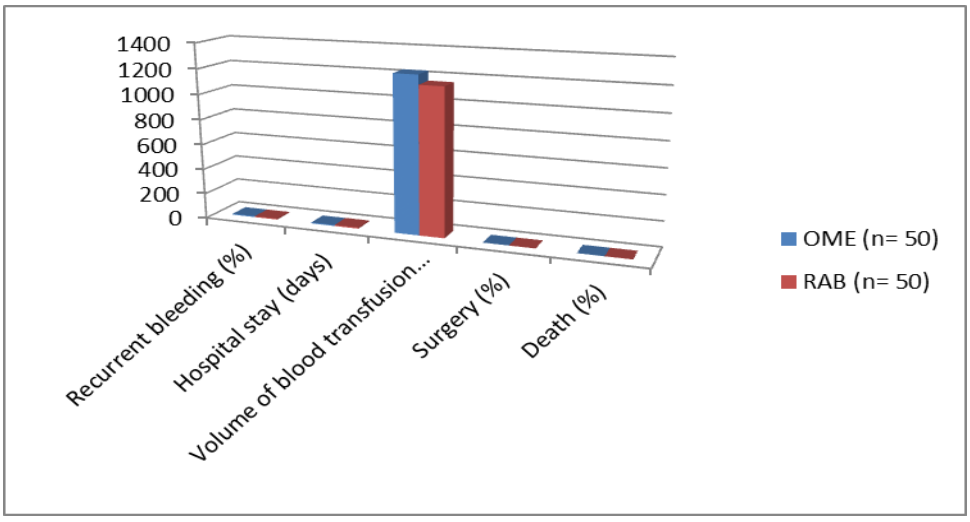


Graph 1: Clinical variables of patients at entry to the study.

Table 2 shows the clinical outcomes of this study. Rebleeding occurred in 12 (15.4%) patients in the OME group and 13 patients in the RAB group within 14 days (16.7%) (*P*= 0.83). All rebleeding episodes occurred within 3 days of enrolment. If patients with adherent clots were excluded, the rebleeding rates in the RAB (11/51, 21.6%) and OME groups (11/55, 20%) were still comparable (*P*= 0.87).

Table 2: Clinical outcomes of patients according to routes of PPI.

	OME (*n*= 50)	**RAB (*n*= 50)**
Recurrent bleeding (%)	8 (15.4%)	8 (16.7%)
Hospital stay (days)	8.5 (7.4, 9.6)	8.9 (7.3, 9.7)
Volume of blood transfusion after therapy (ml)	1231 (487, 1995)	1156 (489, 1569)
Surgery (%)	1 (1.3%)	1 (1.3%)
Death (%)	1 (1.3%)	1 (2.6%)



Graph 2: Clinical outcomes of patients according to routes of PPI,

Rebleeding occurred in 12 patients (15.4%) in the OME group. Of these patients, seven received heater probe therapy plus epinephrine injection and recovered uneventfully, two received a second epinephrine injection and recovered uneventfully, three received haemoclip placements, and two recovered uneventfully, while the third received surgical intervention due to continuous bleeding.

Rebleeding occurred in 13 patients (16.7%) in the RAB group. Of these patients, four received heater probe therapy plus epinephrine injection and recovered uneventfully, four received a second epinephrine injection and recovered uneventfully, three received haemoclip placements and recovered uneventfully, one received transarterial embolization and recovered uneventfully, and one received surgical intervention due to massive rebleeding.

The mean volume of blood transfusion was 1231 ml in the OME group, not significantly different from that of 1156 ml in the RAB group ($P > 0.1$). The mean duration of hospital stay was 8.52 days in the OME group and 8.86 days in the RAB group ($P > 0.1$). One patient died of unrelated illness in the OME group (pneumonia and sepsis), whereas two patients in the RAB group died of unrelated illness (necrotizing fasciitis and sepsis in one patient, terminal lung cancer in the other patient) (1.3% *vs.*2.6%, $P= 1.0$). The mortality and surgical rates were identical at 14 days and 30 days of enrolment.

DISCUSSION

The most important finding of our study is that oral and i.v. administrations of PPI were equally effective as adjuvant pharmacotherapy for patients with high-risk bleeding ulcers. This is the first controlled trial to demonstrate that the clinical outcomes, including rebleeding, blood transfusion, surgery, hospital stay and mortality, are comparable in patients receiving oral and i.v. PPI in the setting of peptic ulcer bleeding with high-risk stigmata.

PPIs increase intragastric pH and thereby help the formation and stabilization of the blood clots, since gastric acid impairs haemostasis by promoting platelet degradation and fibrinolysis.[26] Previous clinical trials had confirmed the effectiveness of PPI in reducing recurrent bleeding, surgery and mortality in patients with high-risk bleeding ulcers[7–12], but the optimal route and dosage of PPI administration remained controversial.[11–16]

Oral PPI has been shown effective in improving clinical outcomes in patients with peptic ulcer bleeding. Khuroo and colleagues have shown that the recurrent bleeding rate was

reduced from 36.4 to 10.9% ($P < 0.001$) in patients with NBVV who received oral omeprazole 40 mg twice daily for 5 days in a placebo-controlled trial.[17] Javid *et al.* gave oral omeprazole 40 mg every 12 h for 5 days in patients with high-risk peptic ulcers after endoscopic injection of epinephrine plus 1% polidocanol and found that oral PPI was superior to placebo in reducing hospital stay, rebleeding rate, and the need for blood transfusion.[18] Kaviani *et al.* conducted a double-blind, randomized, placebo-controlled trial to confirm the efficacy of oral omeprazole in reducing rebleeding rate.[19]

Currently available evidence does not indicate that oral PPI is inferior to i.v. administration. Andriulli *et al.* evaluated 35 randomized trials that compared PPI with placebo or histamine type 2 receptor antagonist (H2RA) and concluded that the benefits of PPI appeared to be independent of the route and dose of PPI.[20] A Cochrane meta-analysis by Leontiadis and colleagues found no evidence to suggest route of PPI administration influenced the rebleeding, surgery or mortality.[11] A recent 'head to head' comparative trial conducted by Laine *et al.* investigated the ability of oral (120 mg bolus followed by 30 mg every 3 h) *vs.* i.v. (90 mg bolus followed by 9 mg h^{-1}) high-dose lansoprazole to increase intragastric pH above 6. This well-designed study demonstrated that intragastric pH > 6 was maintained for 67.8% of the study period (24 h) in patients with i.v. PPI, and 64.8% in those with oral PPI (95% confidence interval of difference –9.2, 15.2). They concluded that frequent oral PPI may replace i.v. infusion PPI. Nevertheless, this study did not evaluate clinical outcomes as study end-points. Moreover, the laboriously frequent dosing schedule (every 3 h) limited clinical application of their study result.

In our randomized comparative trial, we found that recurrent bleeding, surgery, blood transfusion, and mortality were similar between the oral RAB and i.v. OME groups. The overall rebleeding rate of our study was 16% (15.4% in the i.v. PPI group and 16.7% in the oral PPI group, $P= 0.83$), which was lower than previous studies observed with placebo.[7, 8] Nevertheless, the rebleeding rates of our study appeared to be higher than in those receiving endoscopic and PPI therapy.[6–8] One probable reason and also a major limitation of our study is that we adopted epinephrine injection as the primary haemostatic measure, which might be considered suboptimal for high-risk bleeders.[2, 6, 27] Calvet *et al.* analysed 16 trials comparing epinephrine injection alone with combination therapy (epinephrine injection plus a second endoscopic therapy) and found the rebleeding rate to be 18.4% in the epinephrine alone, significantly higher than 10.6% in the combination therapy.[27] In a meta-analysis evaluating

combination endoscopic therapy *vs.* epinephrine injection, Marmo *et al.* showed recurrent bleeding occurred in 15.58% (*n*= 193) of the pooled 1239 patients with single endoscopic therapy of epinephrine injection.[6] In fact, our results might reflect the poorer efficacy of epinephrine injection. We used epinephrine injection as standardized endoscopic therapy in this study because it is among the most popular endoscopic therapies, and therefore our result could be applied in most hospitals. We did not intend to recognize endoscopic epinephrine injection as the best available therapy. Instead, we excluded those whose haemostasis was not achieved by injection therapy alone, and used thermal or mechanical methods as rescue haemostatic procedures in rebleeding ulcers. On the other hand, our study has revealed that oral and i.v. PPI were similarly effective adjuvant pharmacotherapies even if the endoscopic therapy was limited to epinephrine injection.

Whether dosage of PPI influences clinical effectiveness is another unsettled issue in the management of patients with peptic ulcer bleeding. In a double-blind comparative trial, Udd *et al.* randomized 142 patients to receive i.v. omeprazole with either a regular dose (20 mg once daily) or a high-dose (80 mg bolus followed by 8 mg h^{-1}) in patients with bleeding peptic ulcers (Forrest I–II), and found the rebleeding rates (8.2%) of the regular-dose group was equivalent to that (11.6%) of the high-dose group.[13] They concluded that a regular dose of omeprazole was as successful as a high dose. Similarly, Cheng *et al.* found that low-dose i.v. omeprazole (80 mg day^{-1}) was equally effective as a high-dose (200 mg day^{-1}) in preventing rebleeding in patients after endoscopic therapy (injection with or without thermal therapy).[14] On the other hand, a retrospective analysis by Simon-Rudler and colleagues found continuous infusion of high-dose omeprazole (80-mg bolus followed by 8 mg h^{-1}) was more effective than a standard dose of i.v. omeprazole (40 mg day^{-1}) in the occurrence of rebleeding, death due to haemorrhagic shock, and need of surgery.[15] Meta-analysis studies have not resolved this highly debated issue.[11, 12, 20] At present, we consider the available evidence conflicting in determining the relative effectiveness of a high-dose PPI over a regular dose. Since it was the route rather than the dosage that we aimed to investigate, we had to control the dosage of PPI. We did not consider a third arm of high-dose infusion PPI in order not to make the results difficult to interpret. Further well-designed studies are necessary to elucidate the controversy regarding the dosage of PPI. With the knowledge derived from Laine's and our study[24], we consider a future large factorial study with four arms (high and regular dosage *vs.* i.v. and oral route) may be valuable to better define the dosing method of PPI.

Several limitations of our study should be noted. First, the use of epinephrine injection alone is suboptimal compared with combination endoscopic therapy. In this study we adopted thermocoagulation and mechanical clipping as rescue therapy. Although this might affect the overall rebleeding rate, the impact of endoscopic therapy on clinical outcomes was minimized. Second, this study may be underpowered to detect subtle differences. Because this is the first clinical outcome research to evaluate oral *vs.* i.v. PPI, we assumed oral rabeprazole was comparable to H2RA when compared with i.v. PPI while estimating the sample size. The difference between the two groups turned out to be much smaller than initially expected (25% difference in rebleeding rate), and thus the predefined sample size might not be large enough for a small difference. Post hoc analysis revealed that a sample size as large as 12 515 patients in each arm was needed to detect the difference (15.4% *vs.* 16.7%, with an α level of 0.05 and a power of 0.8). We therefore concluded the two groups were equally effective, but recognized that the predefined sample size might not be large enough for a small difference. Third, our study enrolled Taiwanese patients only. Whether a similar result would have been found in a Western population requires further validation, inasmuch as the ethnic or environmental factors may affect the treatment response.[11, 28]. Fourth, the open-label design of our study might raise some concerns as regards bias. Nevertheless, assessment bias should be negligible because the definitions of end-points were all standardized and objective.

CONCLUSION

This single-centre, prospective, randomized, controlled trial of patients with high-risk bleeding ulcers has shown that oral and i.v. regular-dose PPI were equally effective as adjuvant pharmacotherapy to endoscopic haemostasis. Oral rabeprazole (20 mg twice daily) and i.v. infusion omeprazole (40 mg every 12 h) were not different in recurrent bleeding, surgery, blood transfusion or mortality. Our results suggest that oral PPI may be able to replace i.v. infusion PPI as the treatment of choice in peptic ulcer bleeding. However, more studies, particularly validating trials in Western countries, are necessary before oral PPI can be considered as the standard treatment.

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