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EDITORIAL

Role of proton pump inhibitors in the management of peptic ulcer bleeding

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Abstract

Peptic ulcer bleeding is 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. The efficacy of large-dose proton pump inhibitor (PPI) therapy in reducing re-bleeding after endoscopic therapy has been supported by evidence derived from randomized controlled trials. It may be premature to recommend small-dose intravenous injection PPI after endoscopic hemostasis in patients with bleeding ulcers. An updated systematic review shows that PPI therapy before endoscopy significantly reduces the proportion with major stigmata and requirement for endoscopic therapy at index endoscopy. Some studies show that there is no significant difference between oral and intravenous PPIs in raising intragastric pH. However, clinical data is lacking in patients with peptic ulcer bleeding to date.

Key words: Proton pump inhibitor; Peptic ulcer bleeding; Re-bleeding; Hemostasis; Endoscopic therapy

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Peptic ulcer bleeding remains a serious medical problem with significant morbidity and mortality. Despite advance in management of this life-threatening condition, the mortality rate remains around 5%-10%. 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].

Is adjuvant pharmacotherapy effective in reducing re-bleeding following successful endoscopic therapy? From a theoretical point of view, a stable blood clot in a peptic ulcer is crucial to hemostasis. However, in a low pH environment, platelet dysfunction has been observed[3,4]. In addition, pepsin can lyse the blood clots that plug vessels in the ulcer base and induce re-bleeding thereafter[4,5]. Thus, the hypothesis that by suppressing the intragastric acid, the use of proton pump inhibitor (PPI) might benefit patients at risk for further hemorrhage was proposed.

The efficacy of PPI therapy in reducing re-bleeding has been supported by evidence derived from randomized controlled trials[6]. Findings from meta-analyses suggest that histamine receptor 2 antagonists (H2RAs) might not be as effective as PPIs for this indication[6]. We have previously shown that pharmacological tolerance of H2RAs significantly limits their capability to sustain a high intragastric pH[7]. Therefore, we believe that PPIs should be the drug of choice for the prevention of peptic ulcer re-bleeding as far as therapeutic efficacy is concerned.

With regards to PPIs usage as an adjuvant pharma-

cotherapy in the management of peptic ulcer bleeding, the following questions should be answered: the dosage of optimal action, route of administration (oral or intravenous), mode of intravenous route (continuous infusion or bolus), use before or after endoscopic therapy and which is the choice PPI?

To sustain a high intragastric pH, a high dose of omeprazole has been used in previous studies concerning high-risk peptic ulcer bleeding. In our study, we used 40 mg omeprazole intravenous bolus followed by 160 mg/d continuously infusion for 3 d. The mean intragastric pH rose to 6.0 one hour after the initial bolus of omeprazole in the omeprazole group and it was maintained around this value for the rest of the 24 h[7]. The re-bleeding rates were much lower in the PPI group as compared with the H2RA group (Day 3: 0/50 *vs* 8/50, $P < 0.01$; Day 14: 2/50 *vs* 12/50, $P < 0.01$). In a similar study, Lau *et al*[8] used omeprazole 80 mg intravenous bolus followed by 8 mg/h for 3 d and the re-bleeding rates were also much lower in the PPI group as compared with the placebo group (Day 3: 5/120 *vs* 24/120 $P < 0.001$; Day 30: 8/120 *vs* 27/120, $P < 0.001$).

On the other hand, low dose PPI use was supported by some studies. A 2008 multicenter trial by Andriulli *et al*[9] demonstrated a similar efficacy of high dose PPI (80 mg bolus followed by 8 mg/h) and low dose PPI (40 mg bolus daily) in patients with peptic ulcer bleeding. They concluded that 40 mg omeprazole or pantoprazole daily was as effective as a high-dose regimen in reducing the risk of recurrent bleeding. Cheng *et al*[10] used 7-d low-dose omeprazole (3.3 mg/h) and 3-d high-dose omeprazole (8 mg/h) in patients with peptic ulcer bleeding combined with co-morbid illness. They concluded that prolonged low-dose PPI infusion for 7 d reduce re-bleeding during the first 28 d in these patients.

There are some points that deserve discussion in the Andriulli *et al*[9] and Cheng *et al*[10] studies. Dual endoscopic therapy has been proven significantly superior to epinephrine injection alone for bleeding high-risk peptic ulcers[11]. Epinephrine injection alone cannot seal the bleeding vessels immediately. Therefore, a high re-bleeding rate may occur after epinephrine injection alone[11]. This phenomenon has been observed in our previous studies[12]. Therefore, epinephrine injection is not recommended as the only therapeutic modality for these high-risk patients. Unfortunately, over 50% (50% in intensive regimen and 57.6% in standard regimen) of Andriulli *et al*'s[9] study and over one third of the patients (55/142, 38.7%) in Cheng *et al*'s[10] study received epinephrine injection alone. Under these conditions, results and conclusions may be misleading. Therefore, it may be premature to recommend low-dose intravenous PPI after endoscopic hemostasis in patients with bleeding ulcers[13].

How about the route of PPI usage? Which route (oral or intravenous) is the preferred route? Laine *et al*[14] used oral lansoprazole in patients with peptic ulcer bleeding. Patients were randomly assigned to intravenous lansoprazole (90 mg bolus followed by 9 mg/h infusion) or oral lansoprazole (120 mg bolus followed by 30 mg every 3 h). A pH was recorded for 24 h. Mean pH rose above 6 after 2-3 h of intravenous PPI and 3-4 h of oral PPI. They concluded that frequent oral PPI may be able to replace the currently recommended intravenous bolus plus infusion PPI therapy in patients with bleeding ulcers. In one recent article, Javid *et al*[15] also proved that there was no significant difference among various PPIs (omeprazole, pantoprazole and rabeprazole) given through different routes (intravenous and oral routes) on raising intragastric pH above 6 for 72 h after successful endoscopic hemostasis in bleeding peptic ulcer. In our recent study, we have proved that oral rabeprazole and intravenous omeprazole are equally effective in preventing re-bleeding (13/78 in rabeprazole *vs* 12/78 in omeprazole, $P > 0.1$) in high-risk bleeding peptic ulcers[16]. All secondary outcomes between the two groups were similar including the amount of blood transfusion, hospital stay, need for surgery and mortality.

Is it beneficial to use PPI before endoscopic therapy? Lau *et al*[17] concluded that infusion of high-dose omeprazole before endoscopy accelerated the resolution of signs of bleeding in ulcers (active bleeding: 12/187 in omeprazole group *vs* 28/190 in placebo group, $P = 0.01$) and reduced the need for endoscopic therapy (60/314 in omeprazole group *vs* 90/317 in placebo group, $P = 0.007$). An updated systematic review includes six trials of 2223 patients[18]. PPI therapy initiated before endoscopy in bleeding peptic ulcer patients significantly reduced the proportion with major stigmata (37.2% *vs* 46.5%, $P = 0.005$) and requirement for endoscopic therapy at index endoscopy (8.6% *vs* 11.7%, $P = 0.02$). However, there was no evidence that PPI therapy improves clinical outcomes.

How about the mode of intravenous administration? Should PPI be given as a bolus or continuous infusion? A pooled analysis of 16 randomized controlled trials (> 3800 patients) suggested that optimal effect is achieved with an intravenous 80 mg bolus, followed by continuous infusion of 8 mg/h for 3 d, after which therapy may be continued with an oral PPI. Intermittent bolus administration yielded a minimal benefit[18]. This observation is plausible because intermittent bolus of PPI may cause a big fluctuation of intragastric pH.

Is there any benefit in using PPIs for patients with high-risk patients? Recent meta-analyses showed that use of PPIs significantly decreased the risk of further bleeding [odds ratio: 0.4, 95% confidence interval (CI): 0.24-0.67], the need for urgent surgery (odds ratio: 0.5, 95% CI: 0.33-0.76) and the risk of death (odds ratio: 0.53, 95% CI: 0.31-0.91)[6,19,20].

What is the optimal large dose for intravenous PPI usage? It has been demonstrated that the benefit of PPI appears more pronounced in Oriental patients[21]. This phenomenon can be explained by the low gastric acid output, cytochrome P-450 2C19 genetic polymorphism and high prevalence of *Helicobacter pylori* in Asians. In our recent study, we compared two large doses of intravenous PPIs (160 mg/24 h, $n = 60$ mg/24 h and 192 mg/24 h, $n = 60$) in patients with high-risk peptic ulcer bleeding[22]. Bleeding

recurred in a total of 11 (9.2%) patients, with six (10%) in the 192 mg/d group and five (8.3%) in the 160 mg/d group ($P > 0.1$). All secondary outcomes between the two groups were similar including the amount of blood transfusion (mean: 1179 mL *vs* 1203 mL, $P > 0.1$), hospital stay (mean: 9.5 d *vs* 9.9 d, $P > 0.1$), need for surgery ($n = 1$ *vs* $n = 0$, $P > 0.1$) and mortality ($n = 1$ *vs* $n = 0$, $P > 0.1$). Therefore, we believe that dosage of intravenous PPIs in Asians can be lower than that of Occidentals.

In conclusion, in patients with high-risk peptic ulcer bleeding after successful endoscopic therapy, a large intravenous dose of continuous infusion PPI for 3 d is recommended as the management of choice. Whether the oral route can replace the intravenous route in administering PPI remains to be determined.

REFERENCES

1 **Cook DJ**, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology* 1992; **102**: 139-148

2 Consensus statement on therapeutic endoscopy and bleeding ulcers. Consensus Development Panel. *Gastrointest Endosc* 1990; **36**: S62-S65

3 **Green FW Jr**, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology* 1978; **74**: 38-43

4 **Low J**, Dodds AJ, Biggs JC. Fibrinolytic activity of gastroduodenal secretions--a possible role in upper gastrointestinal haemorrhage. *Thromb Res* 1980; **17**: 819-830

5 **Patchett SE**, Enright H, Afdhal N, O'Connell W, O'Donoghue DP. Clot lysis by gastric juice: an in vitro study. *Gut* 1989; **30**: 1704-1707

6 **Leontiadis GI**, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev* 2006; CD002094

7 **Lin HJ**, Lo WC, Lee FY, Perng CL, Tseng GY. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. *Arch Intern Med* 1998; **158**: 54-58

8 **Lau JY**, Sung JJ, Lee KK, Yung MY, Wong SK, Wu JC, Chan FK, Ng EK, You JH, Lee CW, Chan AC, Chung SC. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000; **343**: 310-316

9 **Andriulli A**, Loperfido S, Focareta R, Leo P, Fornari F, Garripoli A, Tonti P, Peyre S, Spadaccini A, Marmo R, Merla A, Caroli A, Forte GB, Belmonte A, Aragona G, Imperiali G, Forte F, Monica F, Caruso N, Perri F. High- versus low-dose proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding: a multicentre, randomized study. *Am J Gastroenterol* 2008; **103**: 3011-3018

10 **Cheng HC**, Chang WL, Yeh YC, Chen WY, Tsai YC, Sheu BS. Seven-day intravenous low-dose omeprazole infusion reduces peptic ulcer rebleeding for patients with comorbidities. *Gastrointest Endosc* 2009; **70**: 433-439

11 **Marmo R**, Rotondano G, Piscopo R, Bianco MA, D'Angella R, Cipolletta L. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. *Am J Gastroenterol* 2007; **102**: 279-289; quiz 469

12 **Lin HJ**, Lo WC, Cheng YC, Perng CL. Role of intravenous omeprazole in patients with high-risk peptic ulcer bleeding after successful endoscopic epinephrine injection: a prospective randomized comparative trial. *Am J Gastroenterol* 2006; **101**: 500-505

13 **Barkun AN**, Kuipers EJ, Sung JJ. It is premature to recommend low-dose intravenous proton pump inhibition after endoscopic hemostasis in patients with bleeding ulcers. *Am J Gastroenterol* 2009; **104**: 2120-2121

14 **Laine L**, Shah A, Bemanian S. Intragastric pH with oral vs intravenous bolus plus infusion proton-pump inhibitor therapy in patients with bleeding ulcers. *Gastroenterology* 2008; **134**: 1836-1841

15 **Javid G**, Zargar SA, U-Saif R, Khan BA, Yatoo GN, Shah AH, Gulzar GM, Sodhi JS, Khan MA. Comparison of p.o. or i.v. proton pump inhibitors on 72-h intragastric pH in bleeding peptic ulcer. *J Gastroenterol Hepatol* 2009; **24**: 1236-1243

16 **Tsai JJ**, Hsu YC, Perng CL, Lin HJ. Oral or intravenous proton pump inhibitor in patients with peptic ulcer bleeding after successful endoscopic epinephrine injection. *Br J Clin Pharmacol* 2009; **67**: 326-332

17 **Lau JY**, Leung WK, Wu JC, Chan FK, Wong VW, Chiu PW, Lee VW, Lee KK, Cheung FK, Siu P, Ng EK, Sung JJ. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med* 2007; **356**: 1631-1640

18 **Morgan D**. Intravenous proton pump inhibitors in the critical care setting. *Crit Care Med* 2002; **30**: S369-S372

19 **Sung JJ**, Chan FK, Lau JY, Yung MY, Leung WK, Wu JC, Ng EK, Chung SC. The effect of endoscopic therapy in patients receiving omeprazole for bleeding ulcers with nonbleeding visible vessels or adherent clots: a randomized comparison. *Ann Intern Med* 2003; **139**: 237-243

20 **Bardou M**, Toubouti Y, Benhaberou-Brun D, Rahme E, Barkun AN. Meta-analysis: proton-pump inhibition in high-risk patients with acute peptic ulcer bleeding. *Aliment Pharmacol Ther* 2005; **21**: 677-686

21 **Leontiadis GI**, Sharma VK, Howden CW. Systematic review and meta-analysis: enhanced efficacy of proton-pump inhibitor therapy for peptic ulcer bleeding in Asia--a post hoc analysis from the Cochrane Collaboration. *Aliment Pharmacol Ther* 2005; **21**: 1055-1061

22 **Hsu YC**, Perng CL, Yang TH, Wang CS, Hsu WL, Wu HT, Cheng YC, Chiang MF, Lin HJ .Comparable Effectiveness of Two Doses of Continuous Infusion Pantoprazole in Peptic Ulcer Bleeding. *Br J Clin Pharmacol* 2010; 69: 245-251

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