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EDITORIAL

Intravenous proton pump inhibitors for peptic ulcer bleeding: Clinical benefits and limits

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Abstract

Peptic ulcer bleeding is a common disease and recurrent bleeding is an independent risk factor of mortality. Infusion with proton pump inhibitors (PPIs) prevents recurrent bleeding after successful endoscopic therapy. A gastric acidic environment of less than pH 5.4 alters coagulation function and activates pepsin to disaggregate platelet plugs. Gastric acid is secreted by H^+, K^+-ATPase, naming the proton pump. This update review focuses on the mechanism and the role of PPIs in the clinical management of patients with peptic ulcer bleeding. An intravenous omeprazole bolus followed by high-dose continuous infusion for 72 h after successful endoscopic therapy can prevent the recurrent bleeding. In the Asian, however, the infusion dosage can possibly be diminished whilst preserving favorable control of the intragastric pH and thereby still decreasing rates of recurrent bleeding. Irrespective of the infusion dosage of PPIs, rates of recurrent bleeding remain high in patients with co-morbidities. Because recurrent peptic ulcer bleeding may be prolonged in those with co-morbidities, a low-dose infusion of IV PPIs for up to 7-day may result in better control of recurrent bleeding of peptic ulcers. Due to the inter-patient variability in CYP2C19 genotypes, the infusion form of new generation PPIs, such as esomeprazole, should be promising for the prevention of recurrent bleeding. This article offers a comprehensive review of clinical practice, highlighting the indication, the optimal dosage, the duration, and the potential limitation of PPIs infusion for peptic ulcer bleeding.

Key words: Peptic ulcer bleeding; Recurrent bleeding; Comorbidity; Cytochrome P-450 2C19; Proton pump inhibitor; Omeprazole

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INTRODUCTION

Upper gastrointestinal bleeding is a rather common disease with prevalence rates of up to 102 per 100 000 people[1,2]. About 48% of upper gastrointestinal bleeding is related to peptic ulcer diseases[3]. Peptic ulcer bleeding is a potentially lethal disease, and recurrent bleeding is a considered and independent risk factor potentially leading to mortality[4,5]. Recurrent bleeding is positively linked with the presence of stigmata of recent hemorrhage, co-morbidities, and others[1,5-10]. In general, patients with underlying medical

co-morbidities have increased rates of recurrent bleeding and longer duration of risk for recurrent bleeding than those without co-morbidity[6,10].

Because the acid environment of stomach is rather hostile for ulcer healing, the clinical course of peptic ulcer bleeding is more complicated than skin wound bleeding. The recurrent bleeding rate of peptic ulcers varies widely, from as low as only 5% up to almost 100%[11]. Inhibition of gastric acid secretion by intravenous infusion of proton pump inhibitors (PPIs) has now been shown to prevent the recurrent bleeding after successful endoscopic therapy[12-15]. However, the mortality rate of peptic ulcer bleeding has still not decreased even after PPIs usage. Yavorski *et al* found that almost all patients who died from peptic ulcer bleeding have at least one underlying comorbid illness, and the major cause of mortality is thus the underlying comorbid illness which is exacerbated by peptic ulcer bleeding or recurrent bleeding[1]. Accordingly, it is very important to identify high risk patients with comorbidity. For such patients, the more aggressive application of intravenous (IV) PPI could be warranted to control the bleeding and also to prevent recurrent bleeding.

This article offers a comprehensive review of clinical practice highlighting the indication, the optimal dosage, the duration, and the potential limitation of PPIs infusion for peptic ulcer bleeding.

MECHANISM OF PROTON PUMP INHIBITORS

The risk of recurrent bleeding is higher and there is a more complicated healing process in peptic ulcer disease than in cutaneous wounds[11]. The major reason for this is the acid microenvironment of the stomach lumen. Intragastric hydrochloric acid (HCl) which provides the acid microenvironment is secreted by H^+, K^+-ATPase, which is a membrane-bound proton pump in parietal cells. The proton pump is an α, β heterodimer[16]. After parietal cells are activated on receptors, proton pumps translocate from tubulovesicles to the membranes of secretory canaliculi[16-18].

The gastric H^+, K^+-ATPase is an important target for development of drugs to inhibit gastric acid secretion[19,20]. Substitutes benzimidazoles are the first group of anti-secretory drugs, acting *via* inhibition of H^+, K^+-ATPase[21,22]. Omeprazole was the first benzimidazole to be launched for clinical use in the late 1980s[23-25]. Other analogues such as lansoprazole, rabeprazole, pantoprazole and esomeprazole have since been developed. These drugs are generically called PPIs.

PPIs are lipophilic and are inactive in the neutral environment of the bloodstream. After absorption, PPIs cross the plasma membrane, enter and accumulate in the secretory canaliculi of parietal cells, where they are protonated by acid, then converted into the active form, sulfenamide[26,27]. The activated sulfenamide reacts covalently with the cysteine sulfhydryl group on the extracellular surface of the α-subunit, the Src homology group of proton pumps, thus inactivates the pump and inhibits gastric acid secretion[25,28]. PPIs are very specific to inhibition of gastric proton pumps because they are activated only in the acidic environment of the stomach, whereas they are not activated for the similar enzyme found in the colon and the kidney[29].

INDICATIONS OF IV PPIs

Recurrent bleeding is an independent risk factor of mortality[4] and remains at a rate of about 15% to 20% even after endoscopic hemostasis. Therefore, the aim of acute treatment of peptic ulcer bleeding is to reduce recurrent bleeding. For both pharmacological and physiological reasons, anti-secretory drugs should be able to reduce rates of recurrent bleeding, given that bleeding sources are acid-related lesions. Because platelet aggregation and plasma coagulation are both abolished while the intragastric pH is below 5.4[30], adequate and sustained acid inhibition results in avoidance of the deleterious effect of acid secretions and pepsin activation on the hemostatic process.

Intravenous PPIs infusion can prevent recurrent bleeding in patients with high risk factors for bleeding peptic ulcers, such as active oozing, non-bleeding visible vessels, and adherent clots[31,32]. Intravenous omeprazole after endoscopic hemostasis shows better results than either cimetidine or placebo in reducing the rate of recurrent bleeding[12-14,33,34], the need for endoscopic treatment[12,13], the number of surgery[13,34], the need for blood transfusion, and the length of hospitalization[12].

Empirical therapy with intravenous PPIs should be considered in patients awaiting endoscopy. The use of intravenous PPIs before endoscopy in case of upper gastrointestinal bleeding was shown to accelerate the resolution of signs of bleeding in ulcers[35], reduce the need for endoscopic therapy and shorten hospital stay[36]. However, the recurrent bleeding rate, operation rate and mortality rate are similar in patients treated with intravenous PPIs and placebo[3]. Most recently, Tsoi *et al*[37] suggested pre-endoscopic administration of PPIs has a lower cost-effectiveness ratio per endoscopic therapy averted (USD $ 3561) than the placebo (USD $ 4117). Pre-endoscopic administration of PPIs may be cost-effective in certain situations[38,39]. Therefore, omeprazole infusion as an adjunct therapy to endoscopic hemostasis in actively bleeding peptic ulcers has a favorable overall clinical outcome.

IV PPIs FOR ULCER RECURRENT BLEEDING CONTROL

Platelet aggregation under different pH conditions

The major defense against hemorrhage is transient vasoconstriction and the subsequent formation of a platelet plug. In an acidic environment, the coagulation cascade and platelet aggregation are inhibited. Green *et al* showed there is a respective 2-fold and 4-fold prolongation of prothrombin time, activated partial thromboplastin time,

and thrombin time at pH 6.4 and pH 6.0 compared to pH 7.4[30]. More acid conditions result in greater prolongation of these assay times. In an acid milieu, not only the platelet aggregation profile is profoundly inhibited but also disaggregation of stable platelet plugs occurs. The extent of disaggregation is higher at pH 6.1 than at pH 7.3.

Pepsin control of platelet aggregation

Green *et al.* also showed not only the capability of acid to produce alterations in the coagulation cascade, but also the additive effect of pepsin in disaggregating platelets in pH as low as 5.5. At similar pH, the mean total percentage disaggregation is higher in the presence of pepsin than in the absence. In an *in vitro* study, the effect of pepsin on enhancement of platelet disaggregation increases with decreasing pH[30].

Goal of intragastric pH elevation

The acid environment in the stomach both promotes activation of pepsin and exacerbates gastric mucosal damage. Gastric acid-peptic activity exacerbates superficial mucosal damage into deep ulceration[40], interferes the ulcer healing[41], and adversely affects hemostatic mechanisms[30]. The physiological goal is to achieve an-acidity to arrest hemorrhage in acute gastroduodenal mucosal lesions.

Because platelet aggregation and plasma coagulation are both abolished at pH 5.4 *in vitro*, it is important to achieve intragastric pH higher than pH 5.4 to arrest hemorrhage[30]. However, endogenous buffers such as hemoglobin in the gut or tissue buffers may be not able to maintain the pH of gastroduodenal contents at or above the level necessary for hemostatic integrity.

Netzer *et al* tested the antisecretory effect of high-dose intravenous omeprazole, delivered either by infusion or injection, over the critical first 72 h. With omeprazole infusion, they found the percentage of time with intragastric pH 6 is 59% on day 1, 71% on day 2 and day 3[42]. An additional study in India showed that high-dose infusion of PPIs, such as omeprazole, rabeprazole, and pantoprazole achieves an intragastric pH $\geqslant$ 6 within 1 h of administration and which is maintained for more than 98% of the time in bleeding peptic ulcers[43]. Laine *et al* also demonstrated the antisecretory effect of high-dose lansoprazole infusion, which keeps intragastric pH >6 for 67.8% of the time[44].

The optimal dose of IV PPIs

Current guidelines suggest that patients with bleeding peptic ulcers should be treated with an intravenous omeprazole bolus followed by continuous infusion after endoscopic therapy[31]. Andersen *et al* evaluated the effect of an initial loading dose of 80 mg omeprazole in intragastric pH and found that it achieves a fast and sustained increase to above pH 4[45]. Additional studies showed that after an intravenous 80 mg omeprazole bolus, a high-dose continuous infusion, at 8 mg per hour for 72 h, achieves the necessary high intragastric pH-level from the first day to the third day either in healthy subjects[42] or in patients with bleeding peptic ulcers[46]. Four clinical trials suggested therapeutic benefit for high-dose PPIs in reducing recurrent bleeding or in achieving a favorable clinical outcome[12,13,33,34].

Controversy surrounds the optimal dose required to target intragastric pH and recurrent bleeding control. In Denmark, Kiilerich *et al* showed that low-dose omeprazole at 4 mg/h continuous infusion after a bolus of 80 mg is as effective as the high-dose in maintaining a consistent pH of around 4-6. However, for the low dose omeprazole there is considerable inter-subject variability in AUC and in time with intragastric pH $\geqslant$ 4[47]. Nevertheless, although individual intragastric pH response curves are more variable in low-dose omeprazole infusion[48], Udd *et al* showed a low-dose intravenous bolus of omeprazole of 20 mg daily for 3 d could be still as effective as the high-dose infusion in controlling peptic ulcer recurrent bleeding[49]. Because of the smaller parietal cells mass[50] and higher prevalence rate of a poor metabolizer of cytochrome P450 CYP2C19 alleles in Asian populations[51], it is rational to decrease omeprazole dose in these groups. In Taiwan, Sheu *et al* reported that a decreased dosage of omeprazole with an intravenous 80 mg omeprazole bolus followed with 40 mg bolus twice daily for the consecutive three days could maintain a favorable intragastric pH[52] and decrease recurrent bleeding[14]. Another trial in Taiwan also showed that a decreased dosage of omeprazole, 3.3 mg/h infusion or 40 mg injected every 12 h for 3 d could effectively decrease rates of recurrent bleeding[6,53]. An increase in intravenous dosage to 40 mg per 6 h showed marginally better recurrent bleeding control for Asian populations[54].

The infusion duration: at least 3 d and longer for some groups

The recurrent bleeding rate of peptic ulcers is related to the presence of the stigmata of recent hemorrhage[11]. The fading time of non-bleeding visible vessels is around 3 to 6 d[55]. Commonly, recurrent bleeding may develop within 2-3 d[56,57]. Accordingly, the common duration of omeprazole infusion is 3 d, applied after the endoscopic therapy[6,12-14,34,52,58]. Nonetheless, even with continuous infusion of omeprazole for 3 d, recurrent bleeding rates remain high in certain patients such as those with the presence of underlying medical co-morbidities [1,4,6,10,56]. Clinical trials showed that control of recurrent bleeding following 3-day omeprazole infusion is worse in patients with co-morbidities than in patients without co-morbidities[6,10]. Moreover, we reported that the duration of peptic ulcer recurrent bleeding is prolonged up to the 14th day after the first bleeding episode in patients with co-morbidities[6,10]. To prevent recurrent bleeding in such high risk patients, we advocated the therapeutic benefit of a prolonged 7-day course of low-dose intravenous omeprazole which can exert better recurrent bleeding control for up to 1 mo[59].

Patients with co-morbidities often have a high Rockall risk score $\geqslant$ 6, which indicates that the mean hospital day after acute upper gastro-intestinal hemorrhage should be more than 10 d[60]. Thus, the cost of the prolonged

admission required for giving a 7-day course of omeprazole infusion is not significant. It should be emphasized that costs associated with a recurrent bleeding event far outweigh costs of PPIs therapy[61]. The shift to 7-day prolonged low-dose omeprazole treatment does not increase the cost of omeprazole itself, as the amount given is equivalent to 3-day high-dose infusion. Therefore, for such high risk patients, the prolonged duration intravenous PPI should be cost-effective, especially in Asian patients.

Factors related with the poor control of IV PPIs: CYP2C19 story

Several risk factors for recurrent bleeding have been demonstrated in a variety of studies. Inter-patient variability in responsiveness to PPIs therapy may be a factor in failed healing of severe esophagitis[62], and higher recurrent bleeding rates of peptic ulcers[63]. One of the reasons maybe because of different metabolizer phenotypes of (*S*)-mephenytoin 4'-hydroxylase (Cytochrome P-450 2C19), by which omeprazole is metabolized to an inactive form[64,65]. According to the single nucleotide polymorphism and enzyme activity, subjects are divided into extensive metabolizers (EM), intermediate metabolizers, and poor metabolizers (PM). The increasing potency of gastric acid suppression and increasing intragastric pH with oral omeprazole is dependent on the CYP2C19 genotype status in the rank order of homo-EM ≤ hetero-EM ≤ PM[66]. There are pronounced geographic and interracial differences in the distribution of this polymorphism. The prevalence rate of PM in Chinese and Japanese is higher than in Caucasians and African descents[67-73].

In addition to the inter-patient variability in responsiveness to omeprazole therapy, a poor disease background or a poor nutrition status also has negative impact on recurrent bleeding control of peptic ulcers. Patients with two or more co-morbid diseases or with hypoalbuminemia < 3.0 g/dL have a significantly higher risk of recurrent bleeding[6,10]. Emerging evidence suggests that the incidence of idiopathic peptic ulcers, defined as patients without *H. pylori* infection and no exposure to NSAIDs, is high in the West (between 11% and 44%), and is also increasing in the Asia (from 4.2% to 18.8%)[74-79]. More than 70% of idiopathic peptic ulcers have comorbid illnesses, half of which are severe or life-threatening systemic disorders, defined as American Society of Anesthesiology score ≥3[74,80]. Current evidences indicate that idiopathic peptic ulcers increase the risk of ulcer recurrence and bleeding. Two studies in Hong Kong showed the probability of peptic ulcer recurrence or bleeding in either 12-month or 7-year follow-up is higher in patients with idiopathic peptic ulcers than those with *H. pylori* infection after eradication. One of the two factors associated with recurrent bleeding is comorbidity with severe or life-threatening systemic disorders[75,80].

The most important systemic disorders are renal failure, liver failure, and disseminated malignancy[4]. Similarly, a retrospective cohort study found that renal failure and liver disease are two independent prognostic factors of an unfavorable clinical course, including persistent or recurrent bleeding, required interventional therapy, and death[81]. Although most recurrent bleeding develops within 72 h[56,57], uremic patients have a higher delayed recurrent bleeding risk for 7 to 30 d [10,82].

DIFFERENCES BETWEEN THE ORAL AND IV PPIs

The intragastric 24-h median pH is 4.93 in patients taking oral 40 mg omeprazole once daily, which is significantly higher than baseline median pH of 1.68 in *H. pylori*-negative healthy subjects. However, probably because of diurnal rhythm, the intragastric pH in patients on oral omeprazole falls to a median pH of 3.03 during the night period from 22:00 to 06:00[83]. Therefore, oral omeprazole 40 mg once daily does not suppress gastric acid secretion completely throughout the 24 h period [84].

Several studies have shown that oral administration of high-dose PPIs is just as effective in raising the intragastric pH to above 6 and reducing recurrent bleeding as intravenous administration[43,44,53]. To achieve similar acid control, the dose of oral lansoprozole should be 120 mg bolus then 30 mg per 3 h for 8 times. Results had shown intragastric pH is greater than 6 during 64.8% of the study period, which is similar to 67.8% achieved with intravenous lansoprazole 90 mg bolus injection, followed by 9 mg/h continuous infusion. Therefore, frequent oral PPIs therapy may be able to replace bolus plus constant intravenous PPIs infusion for patients with peptic ulcer bleeding[44].

LIMITS OF IV PPIs TO CONTROL BLEEDING

As discussed previously, the intravenous bolus and continuous infusion of PPIs following endoscopic therapy is effective in reducing recurrent bleeding in most patients[6,12-14,34,52,58]. However, not all patients receiving high-dose omeprazole infusion achieve a mean intragastric pH of more than 6. The 30% of patients with high-dose omeprazole infusion who have a mean pH value of less than 6 tend to have a higher recurrent bleeding rate within the first 3 d than those with mean pH values of 6 or greater[63]. This may reflect inter-patient variability in responsiveness to PPIs therapy[62,63].

In addition, the presence of co-morbidities and poor nutrition status such as uremia and hypoalbuminemia are also the significant indicators of a higher recurrent bleeding rate even when applying intravenous omeprazole infusion[6,10,82]. Kamada *et al* found that only one-third of patients with *H. pylori*-negative idiopathic duodenal ulcers may have acid hypersecretion[85]. Moreover, despite favorable intragastric pH control, patients with comorbid illnesses still have higher recurrent bleeding[10]. In addition to PPIs, certain host factors should be identified and corrected to prevent recurrent bleeding of peptic ulcers in

such high risk patients[86].

As described previously, pre-endoscopy administration of PPIs may be cost-effective in certain situations[38,39]. However, pre-endoscopy administration of PPIs cannot replace urgent endoscopy in managing patients with upper gastrointestinal bleeding[31].

Because of inter-patient variability in responsiveness to omeprazole therapy[47,62], there is a need to find a therapy that provides even more effective control of gastric acid secretion and also reduces the variation in acid inhibition between patients. Esomeprazole, the *S*-isomer of omeprazole[87], has an improved pharmacokinetic profile leading to greater acid suppression than that produced by omeprazole, pantoprazole, lansoprazole, and rabeprazole[88]. Because the metabolism of omeprazole is stereoselective, the sum of the intrinsic clearance values is 3 times lower for *S*-omeprazole than for *R*-omeprazole[89-91]. Following an intravenous bolus of 80 mg and then 8 mg/h continuous infusion, the AUCt and Cmax of esomeprazole is higher than that of omeprazole[92]. The inter-subject variability of esomeprazole for AUCt is also significantly lower and time with intragastric pH > 4 is less than with omeprazole. Although similar acid suppression achieved by i.v. esomeprazole and i.v. omeprazole, the former has a tendency for a faster onset of action (2 h shorter to the target pH > 6) and significantly lower variability in pharmacodynamic response than the later[92]. Moreover, the median intragastric pH of esomeprazole 40 mg i.v. is significantly higher than that of pantoprazole 40 mg i.v. infusion and bolus injection[93]. The duration to achieve elevation of pH > 4 is longer in the former than in the later (1.7 h *vs.* 0.6 h, $P < 0.0001$)[94].

In clinical studies, the greater acid suppression produced by esomeprazole has been translated into higher healing rates and more effective symptom relief when compared to other PPIs in patients with gastro-esophageal reflux disease[95-98]. In a multiethnic study, Sung *et al* showed the high-dose intravenous esomeprazole infusion given after successful endoscopic therapy to patients with high-risk peptic ulcer bleeding has a lower recurrent bleeding rate and a better clinical outcomes than placebo[99]. Therefore, because the variability in the pharmacodynamic response of intravenous esomeprazole is lower, intravenous esomeprazole could be applied in different CYP2C19 genotypes in preventing recurrent bleeding. However, clinical benefits of intravenous esomeprazole for high risk patients such as those with co-morbidities should be further investigated.

CONCLUSION

In summary, an intravenous omeprazole bolus followed by high-dose continuous infusion for 72 h after successful endoscopic therapy has been shown to inhibit gastric acid secretion effectively and have clinical benefits on the prevention of recurrent bleeding in most patients. In the Asian, low-dose omeprazole infusion can effectively decrease rates of recurrent bleeding. Nevertheless, patients with co-morbidities such as renal failure, liver disease, and hypoalbuminemia or who are extensive metabolizers of CYP2C19 genotype may experience higher rates of recurrent bleeding. The prolonged 7-day course of low-dose intravenous omeprazole may decrease recurrent bleeding in such patients with medical comorbidities. There is a need to validate whether intravenous esomeprazole can improve the control of peptic ulcer recurrent bleeding, especially for patients with different CYP2C19 genotypes and with underlying comorbidities.

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