

## Original Article

# Perioperative application of proton pump inhibitors to prevent stress ulcer

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**Abstract:** Background: Patients with surgeries are prone to the occurrence of stress ulcer when under the stress status. Currently, proton pump inhibitors (PPI) are often used in clinical surgeries to prevent stress ulcer (SU). Purpose: To assess the rationality of perioperative application of PPI to prevent SU. Methods: Two hundred and thirty-eight patients performing surgeries in the department of vascular surgery were enrolled in this study, and 204 patients applied PPI to prevent the perioperative SU. Their basic situations and rationalities of PPI application in these 204 patients were analyzed. Results: The ratio of perioperative PPI application in preventing SU was 85.71% (204/238), while only 47.06% (96/204) of patients had the risk factors of SU. 96.08% (196/204) of administration routes were intravenous. 87.06% (222/255) of PPI injection medical orders selected normal saline as appropriate solvent of PPI. The problems such as too large dosage, long duration and frequent medication-change still existed for PPI application. Conclusion: When applying PPI to prevent SU, there still exist further optimization in aspects such as indications, drug selection, administration routes and dosage.

**Keywords:** Proton pump inhibitors, rational medication, stress ulcer, perioperative

## Introduction

Patients with surgeries are prone to the occurrence of stress ulcer (SU) when under the stress status, including acute postoperative multiple gastric erosions, ulcer and other diseases, thus causing gastrointestinal bleeding, perforation, even deteriorating the original lesions. The preventive effects of SU would directly impact the prognosis of primary diseases. Therefore, perioperatively preventing the occurrence of SU would be particularly important. Currently, the drugs used in clinical surgeries to prevent SU included acid-suppressing drugs, antacids, and mucosal protective drugs. Among acid-suppressing drugs, proton pump inhibitors (PPI) could inhibit the final path of H<sup>+</sup>/K<sup>+</sup>-ATP enzyme, thus inhibiting the secretion of gastric acid. Their acid-suppressing effects were good and safe. Therefore, they had been widely used in treating and preventing gastrointestinal ulcers and bleeding clinically.

Though PPI had strong and definite acid inhibitory effects, the problem of abuse was also serious [1]. Certain survey showed that two-

thirds of patients lacked clear indications when applied PPI [2], and the problem of long duration was also widespread, for example, after patient was transferred outside ICU or discharged from hospital, PPI was still used in the absence of risk factors [3, 4]. The unrational application of PPI not only consumed a lot of health care resources, but also caused adverse reactions induced damages, which might also prolong the duration of hospitalization, and increase health care costs. The main serious adverse reactions included osteoporosis and related fractures, hypomagnesemia, community-acquired pneumonia, pseudomembranous colitis, etc. [5-10]. Furthermore, it was also reported that lansoprazole caused acute interstitial nephritis [11]. Currently, the risk factors mentioned in the guide towards SU included mechanical ventilation, coagulopathy, sepsis, organ failure, shock, severe trauma (traumatic brain injury, burns, major surgery, etc.), age > 65 years old, drug factors (hormones, anticoagulants, immunosuppressants, non-steroidal anti-inflammatory drugs), etc. [12-15]. The preventive drugs mainly included acid-suppressing drugs (PPI, histamine-2 receptor antagonists (H2RA)), antacids (aluminum hydroxide, hydro-

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**Table 1.** Surgery position, surgery method and surgery cases

Position	Method	Number of cases
Peripheral vessels	Artificial and arteriovenous fistula	4
	High ligation of great saphenous vein + endarterectomy	81
	Artery stripping	20
	Arterial thrombosis removal	27
	Resection of hemangioma	5
	Lower extremity venous catheterization/removal	16
	Stent implantation	18
	Filter placement/removal	31
	Radiography	60
Mesenteric vessels	Superior mesenteric arterial thrombosis removal	2
	Intestinal anastomosis	2
	Radiography	1
Extracranial vessels	Carotid artery intima stripping	14
	Plaque resection	12
	Hemangioma resection	2
	Stent implantation	3
	Exploration of carotid artery	1
	Radiography	8

talcite, 5% sodium bicarbonate) and mucosal protective agents (misoprostol), as for severe trauma, high-risk groups, PPI could more stably increase intragastric pH than H2RA, and its effects in reducing the bleeding risk of SU were significantly better than H2RA [16]. In addition, compared with H2RA, it might exhibit more cost-performance effects in severe patients when applied PPI to prevent SU [17]. As for medication timing and duration of administration, the patients proposed for major surgeries and estimated the concurrent potential of SU might be orally administrated PPI before surgery. But since there was no specified dose and timing, as well as no clearly defined selection of species, currently, the preventive medication of PPI before surgery was still much more confused in clinical practice. This study assess the rationality of PPI application in preventing perioperative SU in the department of vascular surgery, aiming to provide a reference for clinical application of PPI.

### Subjects and methods

#### Subjects

Two hundred and thirty-eight patients performing surgeries in the department of vascular surgery of our hospital from January 1, 2014 to June 30, 2014 were enrolled in this study, and 204 patients applied PPI to prevent the

perioperative SU were included. Inclusion criteria: applied perioperative PPI to prevent SU. Exclusion criteria: i) diagnosed as gastrointestinal bleeding when admitted or during the hospitalization; ii) with esophagitis or gastroesophageal reflux disease; iii) with a current history of peptic ulcer. This study was approved by the ethics committee of the Fifth Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants.

#### Contents of rationality evaluation

The contents of rationality evaluation were as follows: l) Whether there existed the risk factors. The diagnostic criteria was that whether there existed the risk factors of SU: (a) respiratory failure (mechanical ventilation > 48 h); (b) blood coagulation disorders (PLT <  $50 \times 10^9$  /L or INR > 1.5); (b) with major surgery (or surgical time > 4 h); (d) with severe trauma; (e) with severe burn (burn area > 35%); (f) with severe traumatic brain injury, spinal cord injury, Glasgow Coma SCORE  $\leq 10$  (or could not execute simple commands); (g) with sepsis; (h) with multiple organ failure; (i) after organ transplantation; (j) associated with shock or sustained hypotension; (k) with liver failure; (l) with acute renal failure; (m) with myocardial infarction; (n) with obstruction; (o) applied high-dose glucocorticoids (equivalent to 250 mg/d or more hydrocortisone); (p) with a history of pep-

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**Table 2.** PPI solvent selection<sup>a</sup>

	Pantoprazole		Lansoprazole		Omeprazole		Esomeprazole	
	NS	GS	NS	GS	NS	GS	NS	GS
iv	4	0	2	0	6	0	2	0
ivgtt	158	24	19	3	30	3	3	1

<sup>a</sup>Number of PPI injection medical order. iv, intravenous; ivgtt, intravenous glucose tolerance test; NS, normal saline; GS, glucose and saline.

**Table 3.** PPI dosage selection (mg)

	Pantoprazole	Lansoprazole	Omeprazole	Esomeprazole
Max daily dosage	160	60	80	80
Min daily dosage	40	30	20	20
Average daily dosage	66.32	42.50	50.21	60.00

**Table 4.** PPI administration frequency<sup>a</sup>

	Pantoprazole	Lansoprazole	Omeprazole	Esomeprazole
Once daily	202	10	29	3
Twice daily	64	14	17	5
Thrice daily	0	0	1	0

<sup>a</sup>Number of PPI medical order.

tic ulcer or digestive tract bleeding within 1 year; (q) with intragastric low pH (pH < 1.30; (r) elderly (aged ≥ 65 years); (l) Whether the dosage and administration was rational.

### Results

#### Basic information of patients

In 238 patients performing surgeries, 204 patients (85.71%, 204/238) perioperatively applied PPI for SU prevention. In 204 patients, there were 133 males (65.20%, 133/204) and 71 females (34.80%, 71/204). The oldest patient was 94 years old, while the youngest patient was 15 years old. The median age was 59±4.5 years. The surgery position, surgery method and surgery cases were shown in **Table 1**. 43 patients received more than two kinds of surgery during the hospitalization. In 204 patients, the ratio of postoperative application was 97.06% (198/204), and the ratio of both preoperative and postoperative application was 2.94% (6/204). No perioperative SU occurred in these 204 patients.

#### Drug selection procedure

During treatment process, the applied PPI included omeprazole, pantoprazole, lansoprazole

and esomeprazole. A total of 345 PPI medical orders were issued, including 266 cases of pantoprazole, 47 cases of omeprazole, 24 cases of lansoprazole and 8 cases of esomeprazole. 255 cases were treated by injection, and 90 cases were treated with oral administration. Analyzed from the cases, it could be seen that 116 patients applied one single PPI, and 86 patients changed PPI during the treatment (including variety, dosage form, manufacturer, solvent, dosage, administration method).

#### Drug administration route

In 204 patients, 8 patients applied single oral PPI, including 5 patients out of the 32 patients without fasting or risk factor. The others applied PPI including oral administration and injection.

#### Solvent for PPI

Among the 255 PPI injection medical orders, the ratio of using 0.9% sodium chloride injection (normal saline) was 87.06% (222/255), and the ratio of using 5% glucose injection (glucose and saline) was 12.16% (31/255) (**Table 2**).

#### Dosage and administration frequency

The PPI dosages varied greatly, and the average daily dosage was more than the conventional daily dosage of each drug (**Table 3**). As for the administration frequency, 244 medical orders were once daily, while the other 101 medical orders were twice or more daily (**Table 4**).

#### Treatment duration

Among the 204 patients, the shortest course was one day, and the longest course was 29

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**Table 5.** Distribution of risk factors for SU

SU risk factor	Cases (n)
Blood coagulation disorder	19
Major surgery (or surgery time > 4 h)	6
Severe traumatic brain injury	1
Application of high-dose corticosteroids ( $\geq 250$ mg/d hydrocortisone)	4
Peptic ulcer/bleeding history within one year	10
Older than 65 years old	73

days, with an average as eight days. The course of 54 patients was  $\leq 3$  days. The course of 54 patients was longer than 3 days while less than 7 days, and the course of 96 patients was longer than 7 days.

### *Risk factors for SU*

One hundred and eight patients had no SU risk factors. 47.06% (96/204) patients had the risk factors of SU, among which 79 patients had one risk factor, 15 patients had two risk factors, and 2 patients had three risk factors. The specific distributions were as shown in **Table 5**.

### **Discussion**

From the applications of PPI, the four kinds of PPI accounted for certain percentages in clinical practice, respectively. The combination of omeprazole and clopidogrel would reduce the effectiveness of clopidogrel, increase cardiovascular events, while other PPI had small interaction with clopidogrel, so the patients with surgery associated with cardiovascular events might choose lansoprazole, esomeprazole and pantoprazole. The effects of lansoprazole were stronger than omeprazole, and could be selected as the first choice in treating acid secretion-related various digestive diseases currently, but it might occasionally cause urinary frequency and proteinuria, so the patients with renal failure should be prohibited. Pantoprazole showed small affinity towards CYP2C19 enzyme, so the patients with mild to moderate liver dysfunction could be applied without dosage reduction, in addition, pantoprazole could also be applied to the patients with kidney dysfunction and elderly patients, its safety and effectiveness when combined with other drugs were higher than omeprazole and lansoprazole, so it was now widely used in clinics, but regarding to its preventive effects towards SU, the intravenous administration of

pantoprazole was equivalent to omeprazole [18]. Esomeprazole was superior to omeprazole, lansoprazole and pantoprazole no matter in onset time, symptom improvements and quality of ulcer healing, but the price was relatively high. Combined with the situa-

tions of the department investigated, PPI selection was basically rational. The investigation revealed the problem of free PPI change, 42.16% of the patients were changed PPI (including varieties, dosage form, manufacturer, solvent, dosage, administration method), and the significance of most these changes was not clear.

Eighty five point seventy one percent of patients with surgery in the department of vascular surgery of our hospital were applied PPI to prevent SU, while only 47.06% (96/204) of patients had clear SU risk factors, and most of them had only one risk factor. It was ruled in "SUP Guidance of American Society of Hospital Pharmacists" [13] that the application of acid-suppressing drugs to prevent SU was only suitable to high-risk groups. The PPI application without indication would cause waste of health resources, so during surgery, the patients should be assessed the risk factors of SU before the application of PPI to prevent unrational usage of PPI.

The prevention of SU in high-risk populations should be recommended oral administration of PPI; the high-risk populations that could not be orally administered might be considered intravenous administration of PPI. One study showed that the high-risk populations with bleeding in endoscopic surgery showed no significant difference between oral and intravenous PPI administration regarding rebleeding rate and average length of hospital stay [19]. 96.08% patients in the department were intravenously administrated, even in the patients with non-high-risk and could eat, the proportion of intravenous PPI administration was as high as 84.38%, which increased patients' medical expenses.

PPI formulations were chemically unstable, belonging to benzimidazole class, and its sulfi-

nyl was susceptible to a variety of factors, such as pH, light, metal ions, and temperature, etc., therefore, when preparing its intravenous infusion, the selection and volume of solvent should be strictly controlled. The specification of omeprazole varieties mentioned that this drug could be dissolved in 100 mL of 0.9% sodium chloride injection or 100 mL of 5% glucose injection; the specifications of pantoprazole, lansoprazole and esomeprazole required no other solvent than 0.9% sodium chloride injection could be used. Because pH of 5% glucose injection was lower than 0.9% sodium chloride injection, while PPI would be decomposed rapidly in acidic solutions, so the stability of 5% glucose injection with PPI was poor, and they were not compatible. 87.06% (222/255) selected appropriate solvent in the department of vascular surgery of our hospital, while the solvent volume was more casual, not strictly in accordance with the preparation instructions.

It was recommended the standard administration was once a day for preoperative prevention; as for high-risk patients, it could be administered in accordance with the standard dose for q12h intravenously. This survey revealed that the initial dose of postoperative PPI therapy was maintained at a higher level, and the ratio of twice or more administration a day was 29.28%, although it was in line with the daily limit of specification in all cases, it increased medical costs for some mild and without-SU-risk-factor patients, reduced the medication compliance, and certain studies indicated that high dosage of PPI was related with the increased mortality in elderly patients [20-23].

As for the patients intended for major surgery and estimated the concurrence of SU postoperatively, preoperative oral administration of PPI could be applied; as for the patients with severe trauma, high risk factors, low-dose intravenous infusion or continuous infusion of PPI should be performed after SU occurred. The course of PPI in preventing SU had not been clearly defied currently, but when patients' conditions became stable, could tolerate enteral nutrition or could eat, and the clinical symptoms began to improve or transferred into general wards, the administration could be changed to oral or gradually withdrawn, thus to avoid long-term administration of PPI caused adverse reactions. It was also

recommended to use other methods to prevent SU, such as intensive care, improving hemodynamics, increasing tissue oxygen saturation, as well as early enteral nutrition.

### Conclusions

Our research found high proportion of perioperative SU prevention in the department of vascular surgery of our hospital, most cases had no clear indication, such as non-major surgery, and non-high-risk groups. The administration methods were most intravenous administration, the daily dosage was relatively large, and the duration was relatively long, in addition, more than 10% of intravenous administration selected wrong solvents. The application of PPI without indication, high-dose and long course increased the financial burdens of patients as well as the risk of drug interactions. Clinical departments should fully master the indications of perioperative PPI application towards SU prevention, and control the dosage and duration within reasonable ranges, so that PPI could be much more safely applied.

### Disclosure of conflict of interest

None.

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