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Retrospective Study

Effect of postoperative use of proton pump inhibitors on gastrointestinal bleeding after endoscopic variceal treatment during hospitalization

Zhang YY *et al.* PPIs after endoscopic variceal treatment

Abstract

BACKGROUND

Endoscopic variceal treatment (EVT) is recommended as the mainstay choice for the management of high-risk gastroesophageal varices and acute variceal bleeding in liver cirrhosis. Proton pump inhibitors (PPIs) are widely used for various gastric acid-related diseases. However, the effect of PPIs on the development of post-EVT complications, especially gastrointestinal bleeding (GIB), remains controversial.

AIM

To evaluate the effect of postoperative use of PPIs on post-EVT complications in patients with liver cirrhosis during hospitalization.

METHODS

Patients with a diagnosis of liver cirrhosis who were admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command and treated by an attending physician between January 2016 and June 2020 and underwent EVT during their hospitalization were included. Logistic regression analyses were performed to explore the effects of postoperative use of PPIs on the development of post-EVT complications during hospitalization. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

RESULTS

Overall, 143 patients were included. The incidence of post-EVT GIB and other post-EVT complications was 4.90% and 46.85%, respectively. In the overall analyses, postoperative use of PPIs did not significantly decrease the risk of post-EVT GIB (OR=0.525, 95%CI=0.113-2.438, $P = 0.411$) or other post-EVT complications (OR=0.804, 95%CI=0.413-1.565, $P = 0.522$). The results remained in the subgroup analyses according to the enrollment period, type and route of PPIs after the index EVT, use of PPIs before the index EVT, use of vasoactive drugs after the index EVT, indication of EVT

(prophylactic and therapeutic), portal venous system thrombosis, ascites, and hepatocellular carcinoma.

CONCLUSION

Routine use of PPIs after EVT should not be recommended in liver cirrhosis for the prevention of post-EVT complications during hospitalization.

Key Words: Endoscopic variceal treatment; Gastrointestinal bleeding; Proton pump inhibitors; Complications; Liver cirrhosis; Acute variceal bleeding

Zhang YY, Wang L, Shao XD, Zhang YG, Ma SZ, Peng MY, Xu SX, Yin Y, Guo XZ, Qi XS. Effect of postoperative use of proton pump inhibitors on gastrointestinal bleeding after endoscopic variceal treatment during hospitalization. *World J Gastrointest Surg* 2022; In press

Core Tip: The role of proton pump inhibitors (PPIs) for the management of post-endoscopic variceal treatment (EVT) complications remains controversial. We have conducted a retrospective study to explore the effects of postoperative use of PPIs on post-EVT gastrointestinal bleeding (GIB) and other post-EVT complications in patients with liver cirrhosis during hospitalization. We found that postoperative use of PPIs was not beneficial for reducing the development of post-EVT GIB and other post-EVT complications during hospitalization. Collectively, routine use of PPIs after EVT during hospitalization may not be worthwhile, and their indications should be carefully evaluated.

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INTRODUCTION

Acute variceal bleeding (AVB) is a serious complication of liver cirrhosis, indicating the disease progression and development of hepatic decompensation^[1,2]. Endoscopic variceal treatment (EVT) is recommended as the major choice for the prevention and

treatment of AVB^[3,4]. However, the incidence of post-EVT gastrointestinal bleeding (GIB) remains 8-25%^[5,6], which is mainly due to recurrent varices and post-EVT ulcers^[7]. In detail, about 4% of patients develop recurrent variceal bleeding after EVT, and 3-25% of patients develop post-EVT ulcer-related GIB^[2,8]. Notably, the mortality of GIB secondary to post-EVT ulcer is as high as 52%^[2].

Considering the benefits of proton pump inhibitors (PPIs) on the prevention of post-EVT GIB^[9,10], the American Society for Gastrointestinal Endoscopy recommends the use of PPIs after endoscopic variceal ligation (EVL) to reduce the rate of ligation-induced ulcer^[11] and the Chinese Medical Association also recommends the postoperative use of PPIs to improve the hemostasis success and reduce the rates of ulcer and recent post-EVT GIB^[12]. Indeed, the clinicians often use PPIs after EVT in clinical practice^[13]. However, the British Society of Gastroenterology states that PPIs are only recommended in the presence of peptic ulcers¹⁴. Additionally, the Baveno VII consensus also states that patients who used PPIs before EVT should discontinue their use immediately after EVT unless they are strictly indicated^[3]. Recent evidence also suggests that the use of PPIs in patients with liver cirrhosis may increase the risk of hepatic encephalopathy and spontaneous bacterial peritonitis^[14]. Therefore, whether the routine use of PPIs after EVT is beneficial remains controversial. For this reason, we conducted a retrospective study to evaluate the effect of postoperative use of PPIs on post-EVT GIB and other post-EVT complications in patients with liver cirrhosis during hospitalization.

MATERIALS AND METHODS

Study design

This study has been approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command with an approval number [Y (2022) 072] and was performed according to the Declaration of Helsinki. The requirement for patients' informed consent for this study was waived due to its retrospective nature. In this

reviewed. The use of PPIs before the index EVT and vasoactive drugs (i.e., octreotide, somatostatin, and terlipressin) after the index EVT were also reviewed. If a patient underwent two or more EVT procedures during the same hospitalization, only the data before the second EVT procedure would be collected.

PPIs after the index EVT

Postoperative use of PPIs was routinely given in all patients who underwent EVT before January 2018. Since then, this attending physician has systematically reviewed the evidence and questioned the clinical significance of use of PPIs following EVT^[10]. Thus, postoperative use of PPIs would be given on demand, if a patient was diagnosed with peptic ulcers, esophageal, gastric, and/or duodenal mucosal erosions, or white nipple signs on endoscopy, developed active variceal bleeding during EVT procedures, or complained of acid-related upper gastrointestinal symptoms (i.e., heartburn and acid regurgitation). Enrollment period, type (i.e., esomeprazole and pantoprazole), route (i.e., intravenous and oral), dosage (i.e., 40mg once daily, 40mg twice daily, and 80mg twice daily), date of starting and discontinuation, and duration of PPIs after the index EVT were reviewed. These data were extracted until post-EVT GIB, the second EVT procedure, or discharge, whichever came first.

Grouping

1 Patients were divided into PPIs and non-PPIs groups. The PPIs group was defined as patients who had started to receive PPIs within 24 h after the index EVT for at least one day before post-EVT GIB, the second EVT procedure, or discharge, whichever came first. The non-PPIs group was defined as patients who had not received PPIs after the index EVT until post-EVT GIB, the second EVT procedure, or discharge, whichever came first (**Figure 1**).

Outcomes

The primary outcome was the development of post-EVT GIB during hospitalization. Post-EVT GIB was defined as the presence of hematemesis, and/or melena, and/or hematochezia, and/or firm clinical or laboratory evidence of acute blood loss from the gastrointestinal tract after the index EVT^[24]. Other post-EVT complications included retrosternal pain/discomfort, nausea/vomiting, heartburn/acid regurgitation, fever, diarrhea, and abdominal pain.

2 Statistical analyses

All statistical analyses were performed on the IBM SPSS 20.0 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as median (range) and mean \pm standard deviation, and categorical variables were expressed as frequency (percentage). The non-parametric Mann-Whitney U test was used to compare continuous variables between PPIs and non-PPIs groups, and the Chi-square test and Fisher's exact test were used to compare categorical variables between the two groups. Logistic regression analyses were performed to explore the impact of postoperative PPIs on post-EVT GIB and other post-EVT complications during hospitalization. Subgroup analyses were performed according to the enrollment period, type and route of PPIs after the index EVT, use of PPIs before the index EVT, use of vasoactive drugs after the index EVT, indication of EVT, PVST, ascites, and HCC (Figure 1). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Overall, 148 patients with cirrhosis underwent EVT during their hospitalization. Finally, 143 patients were included (Figure 2). Of them, 83 were in the PPIs group and 60 in the non-PPIs group. The median duration of PPIs administration was 6 (1-13) days. The median hospital stay since EVT was 6 (2-16) days. Patient characteristics were shown in Table 1. Hepatitis B virus infection alone (36.36%) was the most common etiology of liver cirrhosis followed by alcohol abuse alone (23.08%). The median MELD

score and Child-Pugh score were 10.24 and 6.00, respectively. Eighty (55.94%), 14 (9.79%), 6 (4.20%), 41 (28.67%), 1 (0.70%), and 1 (0.70%) patient were treated with EVL alone, ECGI alone, EIS alone, EVL combined with ECGI, EIS combined with ECGI, and EVL combined with ECGI and EIS, respectively (Table 2).

Overall analyses

Seven (4.90%) patients developed post-EVT GIB, including three in the PPIs group and four in the non-PPIs group. The median interval between the index EVT and post-EVT GIB was 4 (2-7) days. Only one of them underwent endoscopy and found that the source of post-EVT GIB was a post-EVT ulcer. All of them were administered immediately with intravenous vasoactive drugs for the management of post-EVT GIB and two received blood transfusions. Other post-EVT complications were recorded in 67 (46.85%) patients. Logistic regression analyses showed that postoperative use of PPIs was not significantly associated with the risk of post-EVT GIB (OR=0.525, 95%CI=0.113-2.438, $P = 0.411$) (Figure 3) or other post-EVT complications (OR=0.804, 95%CI=0.413-1.565, $P = 0.522$) (Figure 4).

Subgroup analyses

In all subgroup analyses according to the enrollment period, type and route of PPIs after the index EVT, use of PPIs before the index EVT, use of vasoactive drugs after the index EVT, indication of EVT, PVST, ascites, and HCC, logistic regression analyses showed that postoperative use of PPIs was not significantly associated with the risk of post-EVT GIB (Figure 3) or other post-EVT complications (Figure 4).

DISCUSSION

PPIs are one of the most commonly used drugs in the world^[25]. Increasing evidence suggests that the use of PPIs may reduce the abundance and diversity of gut microbiota, leading to the growth of pathogens and the overgrowth of unhealthy species, and that it may be associated with bone fracture, clostridium difficile infection, spontaneous

bacterial peritonitis, and hepatic encephalopathy^[25,26]. These harms have raised serious concerns about the rational use of PPIs worldwide^[27]. Therefore, the clinicians should carefully consider the postoperative use of PPIs during hospitalization, and the investigators should assess the optimal effective dosage and duration of PPIs to avoid their related side effects.

¹³ Our study found that postoperative use of PPIs had no significant effect on post-EVT GIB and other post-EVT complications. Our study has several advantages in terms of study design. First, all patients were diagnosed and treated by the same attending physician and all EVT procedures were also performed by the same endoscopist, which avoids heterogeneity in the management of patients. Second, both patients who underwent prophylactic and therapeutic EVT procedures were included. Third, ⁴ subgroup analyses were comprehensively performed according to the enrollment period, type and route of PPIs after the index EVT, use of PPIs before the index EVT, use of vasoactive drugs after the index EVT, indication of EVT, PVST, ascites, and HCC, which minimizes the impact of confounding factors on statistical results. Fourth, all included patients had been evaluated for at least 24 h since the index EVT, which potentially rules out the effect of technical failure on patients' outcomes.

Post-EVT ulcer, which is one of the main causes of post-EVT GIB, is primarily due to early slippage of rubber bands, sclerosant-induced inflammatory necrosis, and tissue glue-induced caseous necrosis^[7,28-31]. It has been traditionally believed that the presence of gastric acid delays ulcer healing^[32]. Esophageal motility may be temporarily impaired due to nerve plexus injury after EVT, which delays gastric acid clearance and aggravates the progression of ulcers^[33,34]. PPIs are potent acid inhibitors widely used for various acid-related diseases and may promote early healing of post-EVT ulcers by reducing gastric acid secretion, thereby probably decreasing the risk of post-EVT GIB^[26,32,35]. By contrast, our study did not demonstrate the benefits of postoperative PPIs in reducing the development of post-EVT GIB. There are some explanations for

this unexpected phenomenon. First, post-EVT ulcers are more prone to develop bleeding primarily due to persistent portal hypertension, but not gastric acid^[4,31]. Second, the use of PPIs can only reduce the size of ulcers, but not the number of ulcers^[36]. Notably, the size of ulcers is not associated with the risk of bleeding^[36]. Third, we only observed the impact of short-term use of PPIs on the development of post-EVT GIB during hospitalization. However, post-EVT ulcer healing often requires a duration of about 2 wk^[37,38].

Our previous meta-analysis showed a significant benefit of PPIs on post-EVT GIB in patients who underwent prophylactic EVL, but not therapeutic EVT^[10]. However, the present study could not confirm the protective effect of postoperative use of PPIs on GIB after prophylactic EVT, because none of the patients who underwent EVT for primary or secondary prophylaxis of variceal bleeding developed post-EVT GIB. Regardless, it has been proposed that post-EVL ulcers are usually shallower with only superficial mucosal damage, which may heal more easily under the use of PPIs^[37]. Patients who need EVT for the treatment of AVB often have a white nipple, red nipple, or mucosal erosion on endoscopy. Undoubtedly, their conditions are more severe, where the anti-acid effect of PPIs may be insufficient for the improvement of ulcer healing^[4].

Except for post-EVT GIB, EVT can also cause other procedure-related complications, which are mild and reversible^[3,7]. We did not find any significant effect of PPIs on the development of other post-EVT complications. This can be explained by the fact that only a fraction of post-EVT complications, such as acid regurgitation and heartburn, are related to gastric acid^[39]. By comparison, retrosternal discomfort/pain, nausea, and vomiting are mostly mechanical injuries caused by EVT, and fever may be secondary to bacterial infection^[40,41]. Indeed, Grag *et al* also achieved similar findings^[28], but Lo *et al* showed fewer complications in patients receiving PPIs^[42]. Such a discrepancy might be

related to the type of complications evaluated, endoscopic techniques, and patients' conditions.

⁶ Our study has some limitations. First, the total number of the patients included was relatively small in this study. Second, the number of post-EVT GIB was small, which made our statistical analyses underpowered and increased the possibility of type II errors (i.e., false-negative findings). Third, only one patient who developed post-EVT GIB underwent second-look endoscopy, because all of the six patients who developed post-EVT GIB were successfully treated with pharmacotherapy. Fourth, none died of post-EVT GIB or other causes during hospitalization, compromising further analyses regarding the impact of PPIs on death. Fifth, follow-up data were lacking to assess 6-week and long-term mortality.

CONCLUSION

Our study suggested that postoperative use of PPIs could not be supported for reducing the development of post-EVT GIB and other post-EVT complications during hospitalization. Therefore, PPIs after EVT should not be routinely used during hospitalization, and their indications should be carefully evaluated.

ARTICLE HIGHLIGHTS

Research background

Endoscopic variceal treatment (EVT) is often used in cirrhosis with high-risk gastroesophageal varices and acute variceal bleeding. However, it is often associated with a high risk of post-EVT complications, especially postoperative gastrointestinal bleeding (GIB).

Research motivation

The role of proton pump inhibitors (PPIs) after EVT remains controversial.

Research objectives

To evaluate the impact of postoperative use of PPIs on post-EVT GIB and other post-EVT complications in patients with liver cirrhosis during hospitalization.

Research methods

We retrospectively reviewed 911 patients who were consecutively admitted to the Department of Gastroenterology of the General Hospital of Northern Theater Command between January 2016 and June 2020 and treated by an attending physician. Logistic regression analyses were performed to explore the impact of PPIs on post-EVT GIB and other post-EVT complications during hospitalization.

Research results

143 patients were included. The incidence of post-EVT GIB and other post-EVT complications was 4.90% and 46.85%, respectively. In either overall or subgroup analyses, postoperative use of PPIs did not significantly decrease the risk of post-EVT GIB or other post-EVT complications.

Research conclusions

Postoperative use of PPIs was not beneficial for reducing the development of post-EVT GIB and other post-EVT complications during hospitalization.

Research perspectives

PPIs after EVT should not be routinely used during hospitalization, and their indications should be carefully evaluated. Prospective studies can be conducted to further validate the conclusions of this study.

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