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Oral Vonoprazan for Prevention of High-Risk Peptic Ulcer Rebleeding: A Better Alternative Than IV PPIs?

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This summary reviews Geeratragool T, Kaosombatwattana U, Boonchote A, et al. Comparison of vonoprazan vs intravenous proton pump inhibitor for prevention of high-risk peptic ulcers rebleeding after successful endoscopic hemostasis: a multicenter randomized noninferiority trial. Gastroenterology 2024; In Press. https://doi.org/10.1053/j.gastro.2024.03.036

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STRUCTURED ABSTRACT

Question: Is vonoprazan 20 mg oral twice per day (bid) non-inferior to intravenous (IV) pantoprazole 8 mg per hour to reduce recurrent peptic ulcer bleeding in high-risk patients after achieving endoscopic hemostasis?

Design: A multicenter, unblinded, non-inferiority, randomized trial.

Setting: Three university teaching hospitals and 3 community hospitals in Thailand.

Patients: Adult patients presenting with nonvariceal upper gastrointestinal (GI) bleeding were screened and recruited. All patients were initially treated with IV bolus of 80 mg pantoprazole followed by continuous infusion of IV pantopra-

zole 8 mg per hour prior to upper endoscopy. Patients found to have pulsatile ulcer bleeding (Forrest Ia), oozing from a visible vessel in ulcer (Forrest Ib) or a non-bleeding visible vessel in ulcer (Forrest IIa) underwent endoscopic hemostasis with combinations of hemoclipping, thermal therapy with bipolar probe coaptation or argon plasma coagulation with or without injections of adrenaline at the discretion of the endoscopist. Individuals with adherent clot over peptic ulcer (Forrest IIb) had the clot vigorously irrigated or removed with forceps or cold snare and then reclassified prior to endoscopic hemostasis. If clot could not be removed, then patient remained in the study.

Exclusion criteria included in-hospital upper GI bleeding, advanced malignant disease, pregnancy, history of upper GI bleed in past month, or concurrent source of upper GI bleeding (e.g., Mallory-Weiss tear).

Interventions/Exposure: After endoscopic hemostasis was achieved, patients were randomized to receive oral vonoprazan 20 mg bid for 3 days and then continued for 28 days at 20 mg vonoprazan daily vs continued IV pantoprazole at 8 mg per hour for 72 hours, and then converted to oral omeprazole 20 mg bid for 28 days.

Randomization performed based on computer-generated 1:1 block of 4 randomization without stratification. Concealment of allocation maintained by using sealed, opaque, consecutively numbered envelopes with treatment assignment. Study was unblinded.

Outcome: The primary outcome was the 30-day re-bleeding rate while 3-day re-bleeding rate and 7-day re-bleeding rate were secondary outcomes. Confirmation of re-bleeding first required presence of fresh hematemesis > 200 ml or fresh hematochezia/melena after stool color had normalized plus hypotension (systolic blood pressure < 90 mm Hg) or tachycardia (heart rate > 100 beats per minute) with melena or decrease in hemoglobin by > 2 gm/dl with melena. If these findings were present, then a repeat upper endoscopy was required to confirm re-bleeding with endoscopic findings of active bleeding from Forrest Ia or Forrest Ib peptic ulcer or Forrest IIb peptic ulcer with blood or blood clots in the stomach or duodenum.

Data Analysis: Intention-to-treat (ITT) analysis and per protocol analysis was performed. ITT analysis also used to calculate Kaplan-Meier curves for time-to-event

analysis. Sample size was calculated assuming that the re-bleeding rate during first 3 days of IV pantoprazole use would be 7.7% and would be 6.4% during remaining days of oral omeprazole use and that rates of re-bleeding would be similar among the oral vonoprazan group and the oral omeprazole group. A margin within 10% via the Farrington and Manning Test would confirm non-inferiority.

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Results: Between September 2021 and March 2023, over 1,600 individuals with acute upper GI bleeding were screened, and 214 had lesions at high-risk for peptic ulcer re-bleeding (Forrest Ia, Ib, IIa, IIb). Twenty of these patients were excluded due to inability to achieve endoscopic hemostasis, multiple organ failure, or concomitant upper GI bleeding from another cause. Among the 194 study patients that were randomized and included for analysis (vonoprazan group = 98 and IV pantoprazole group = 96), mean age was 66, male 70%, and endoscopic finding of Forrest 1a (splurting bleeding) =2%-4%, Forrest 1b (oozing bleeding) = 10%-12.5%, Forrest IIa (non-bleeding visible vessel) = 85%-78%, and Forrest IIb (adherent clot) = 3%-5%. Most common interventions for endoscopic hemostasis were adrenaline injection with bipolar gold probe coaptation (74%) and adrenaline injection plus hemoclip (17%).

The 3-day, 7-day, and 30-day re-bleeding rates with oral vonoprazan were numerically lower and non-inferior to IV pantoprazole (**Table 1**). In sub-group analysis, the 30-day re-bleeding rates were not found to be significantly different when classified by Forrest classification, aspirin use, study site, or Charlson comorbidity index. Among peptic ulcers that re-bled in both groups, most were large Forrest IIa (non-bleeding visible vessel) ulcers located in the duodenal bulb. In the Kaplan-Meier analysis, time to re-bleeding event was numerically lower with oral vonoprazan vs IV pantoprazole, although this was not statistically significant:

Re-bleeding rates	Vonoprazan oral	Intravenous pantoprazole
Day 3	3.1% (3/98)	6.3% (6/96)
Day 7	5.1% (5/98)	8.3% (8/96)
Day 30	7.1% (7/98)	10.4% (10/96)

Table 1. Re-bleeding rates at day 3, 7, and 30.

COMMENTARY

Why Is This Important?

Current standard of care for patients with upper GI bleeding is to provide high-dose proton pump inhibitors (PPIs), usually as an IV bolus of 80 mg IV pantoprazole followed by a continuous infusion of 8 mg per hour pantoprazole. This is largely because in vitro studies demonstrated that clot-lysis by pepsin could be minimized if the gastric pH >4. Furthermore, in vitro studies demonstrate that platelet aggregation is enhanced when gastric pH approaches 7.[1-3] This laboratory finding led to the use of oral and IV PPIs to reduce recurrent peptic ulcer bleeding by stabilizing clots, especially after endoscopic hemostasis of high-risk ulcers,[1-2] and multiple double-blind, placebo-controlled randomized controlled trials (RCTs) confirmed the benefit of PPIs. However, guideline recommendations provide some nuances about dosing and administration of PPIs for this indication.

Current ACG guidelines[1] recommend high-dose PPI therapy be given continuously or intermittently for 3 days after successful endoscopic hemostatic therapy of a bleeding ulcer (Strong Recommendation, Moderate to High-Quality Evidence) but the authors note that there is not a recommendation for or against for pre-endoscopic PPI therapy for patients with upper GI bleeding. In other words, there is insufficient RCT data to demonstrate benefits of starting PPI therapy when a patient initially presents upper GI bleeding. This is understandable because this initial treatment would only benefit Forrest IIb ulcers (ulcer with adherent clot). Also, although increasing gastric pH with PPIs is beneficial AFTER endoscopic hemostasis (probably by maintaining clot integrity over the ulcer) based on RCT data, the ACG guideline does not clearly recommend IV vs oral administration of PPIs or IV continuous vs intermittent dosing. That's because different RCTs have used different dosing and administration protocols, laboratory studies produce varying results about how high gastric pH can be raised by different oral and IV regimens of PPIs, and also because we're not sure if it's crucial to raise gastric pH to 7, which facilitates platelet aggregation and clot integrity or if we simply need to raise gastric pH >4 to minimize clot lysis by pepsin.[1,3]

Vonoprazan, a potassium-competitive acid blocker which was marketed for erosive esophagitis and *Helicobacter pylori* infection in 2024, may offer an alternative to PPIs for reducing recurrent peptic ulcer bleeding. In randomized crossover studies of 20 mg vonoprazan daily vs 30 mg lansoprazole daily,[4] vonoprazan demonstrated significantly longer half-life (7.9 hours vs 1.5 hours), increased time with gastric pH >4 on day 1 (62.4% vs 22.6%), improvement in gastric acid suppression within 2.5 hours, and was over 100x more potent at acid suppression than

lansoprazole with a mean gastric pH = 5.9 by day 7. Thus, it seems likely that vonoprazan bid would be non-inferior or even superior to IV pantoprazole in high-risk peptic ulcer patients.

Key Study Findings

The 3-day (3.1% vs 6.3%), 7-day (5.1% vs 8.3%), and 30-day re-bleeding rates (7.1% vs 10.4%) with oral vonoprazan were numerically lower and non-inferior to IV pantoprazole (**Table 1**).

Caution

Since the study was unblinded, investigators could be biased in their interpretation of subjective outcomes (e.g., hematemesis or residual blood in stomach). Also, this was designed as a non-inferiority trial, so the sample size is inadequate to determine if oral vonoprazan could be superior to IV pantoprazole. Finally, since much of this study was conducted during the COVID-19 pandemic, median time to endoscopy after initial presentation was longer than originally anticipated: 27 hours (interquartile range: 18-49). This probably led to fewer ulcers being classified as Forrest Ia or Ib and more being classified as Forrest IIa (non-bleeding visible vessel).

My Practice

Based on this RCT, data about the impact of vonoprazan vs proton pump inhibitors on gastric pH[4], and the reduced cost associated with using oral vonoprazan bid vs a continuous intravenous infusion of pantoprazole, I am planning to start using vonoprazan for patients with bleeding peptic ulcers after endoscopic hemostasis.

Based on our current hospital protocols, we initially treat patients with upper GI bleeding with an IV bolus of 80 mg pantoprazole followed by a continuous infusion of 8 mg per hour. This study does not address whether oral vonoprazan could be substituted here, so I may wait for additional data before making further changes.

For Future Research

Larger comparative RCTs with appropriate blinding are needed to determine if oral vonoprazan is superior to IV pantoprazole for reducing recurrent peptic ulcer bleeding after endoscopic hemostasis. Smaller randomized crossover trials that compare gastric pH when patients are treated with vonoprazan 20 mg bid vs intravenous pantoprazole would also be helpful.

Conflict of Interest

Dr. Schoenfeld reports serving as an advisory board member and speaker bureau member for Phathom Pharmaceuticals, manufacturer of vonoprazan.

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