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ORIGINAL PAPER

Prospective, Randomized Trial Comparing Effect of Oral Versus Intravenous Pantoprazole on Rebleeding After Nonvariceal Upper Gastrointestinal Bleeding: A Pilot Study

Jasmohan S. Bajaj · Kulwinder S. Dua · Kristin Hanson · Kenneth Presberg

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Abstract Proton pump inhibitors (PPIs) reduce the rate of rebleeding in patients with nonvariceal upper GI bleed (NVGIB). Oral (PO) and intravenous (IV) pantoprazole are equipotent in raising gastric pH. We conducted a pilot study comparing the efficacy of PO vs. IV pantoprazole for reducing rebleeding after NVGIB. Patients with NVGIB were randomized to receive PO (80 mg BID for 3 days) or IV (80-mg IV bolus and 8 mg/hr infusion for 3 days) pantoprazole followed by pantoprazole, 40 mg PO BID, for 30 days. All patients underwent endoscopy within 24 hr and endotherapy was applied where necessary. Twelve patients randomized to the PO and 13 to the IV pantoprazole group were comparable in age, hematocrit, Rockall scores, ulcer characteristics, and endoscopic interventions. Two patients in the IV arm rebled and another in the IV arm developed reversible renal failure. No patient in the PO arm rebled, had organ failure, or had to be changed to IV pantoprazole. We conclude that in this pilot study, the effect of PO pantoprazole on 30-day rebleeding rate in patients with NVGIB was similar to that of IV pantoprazole.

J. S. Bajaj · K. S. Dua (✉)
Division of Gastroenterology and Hepatology
Medical College of Wisconsin
9200 W. Wisconsin Avenue,
Milwaukee, Wisconsin 53226, USA
e-mail: Kdua@mail.mcw.edu

K. Hanson
Pharmacy Department, Medical College of Wisconsin,
Milwaukee, Wisconsin 53226, USA

K. Presberg
Division of Pulmonary and Critical Care Medicine, Medical College of Wisconsin,
Milwaukee, Wisconsin 53226, USA

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Introduction

Acute nonvariceal upper gastrointestinal bleeding (NVGIB) is a potentially life-threatening condition that often needs intensive care unit support [1]. Resuscitation and endoscopic therapy are the cornerstones in the management of these patients. However, after the initial control of the bleeding, these patients can still rebleed [2]. This can lead to end-organ dysfunction and death. Recent meta-analyses have demonstrated that acid suppression is of benefit in reducing rebleeding rates and that proton pump inhibitors (PPIs) are superior to H_2-receptor blockers in this regard [3]. Studies have shown that PPIs reduce rebleeding rates compared to placebo [4] and endotherapy combined with the use of intravenous PPIs is superior to placebo in reducing the rate of rebleeding in those with NVGIB [5]. Although PPIs are effective in reducing rebleeding after NVGIB, there are no guidelines regarding the optimal route of administration [6].

The intragastric pH increase with oral (PO) pantoprazole is dose dependent and predictable, providing consistent control [7]. A study comparing inhibition of gastric acid secretion of 40 mg PO pantoprazole with that of a similar intravenous (IV) dose showed that they are equipotent in raising the gastric pH [8]. With the exception of a few situations where the patient may not be able to swallow (e.g., patient in a coma), the majority of patients with NVGIB are capable of swallowing a PPI with about half a glass of clear water without interfering with any subsequent endoscopy or surgery. IV PPIs are more expensive than orally administered forms (average wholesale price for IV pantoprazole for a 3-day infusion preparation alone is US$621, compared to US$ 49 for

PO pantoprazole) and require a dedicated IV line that cannot be used for blood or crystalloid and colloid replenishment. There are no systematic studies comparing PO versus IV PPIs in the prevention of rebleeding in patients with NVGIB. We hypothesized that PO pantoprazole would be equivalent to IV pantoprazole in the prevention of rebleeding in patients with NVGIB. In this pilot prospective randomized study our aim was to evaluate the effect of PO versus IV pantoprazole on rebleeding, transfusion requirements, hospital stay, and mortality within 30 days of an acute NVGIB.

Materials and methods

This study was conducted as a pilot trial to evaluate the effect of PO versus IV pantoprazole on rebleeding in patients admitted with NVGIB. The protocol was approved by the Human Research Review Committee at the Medical College of Wisconsin and all subjects gave written informed consent.

Adult (age $\geq$18 years) patients admitted with NVGIB as evidenced by melena or hematemesis were enrolled. Patients were admitted to the intensive care unit (ICU) and underwent esophagogastroduodenoscopy (EGD) within 24 hr of admission, and where necessary endoscopic intervention was performed. We excluded patients with (a) terminal illness, (b) bleeding from tumors or Mallory-Weiss tears, (c) profuse hemorrhage leading to persistent shock (defined as systolic blood pressure of $<$90 mm Hg, pulse rate $>$20 bpm, or end-organ dysfunction) not resuscitatable without interventional radiology and/or surgery, (d) stress ulceration, (e) inability to take oral medication, and (f) allergies to PPI and (g) patients already on PPIs as an outpatient.

The following data were collected from patients at entry: (a) demographic information; (b) comorbid conditions and comorbidity score, e.g., renal disease (serum creatinine $>$2.0 mg/dl), cardiovascular disease (unstable angina, history of myocardial infarction, congestive heart failure), or pulmonary disease (COPD, asthma, pneumonia); (c) Rockall score (validated prognostic score for NVGIB) [9]; (d) recent nonsteroidal anti-inflammatory drug (NSAID)/antiplatelet drug use (within last 1 month); (e) *Helicobacter pylori* serology; and (f) urgent upper endoscopy information, i.e., ulcer location and characteristics such as (i) clean ulcer base, (ii) pigmented spot, (iii) adherent clot, (iv) visible vessel, (v) active bleeding, and (vi) endotherapy if any done (e.g., injection, bipolar coagulation, hemoclip).

The patients were randomized using random numbers to receive either PO or IV pantoprazole. Patients randomized to PO pantoprazole received 80 mg of pantoprazole by mouth 12 hourly, with half a glass of clear water each time, for 72 hr. Patients randomized to the IV arm received IV pantoprazole, 80-mg bolus and then 8 mg/hr infusion, for 72 hr using a dedicated IV line with a filter. After 72 hr, all patients were switched to 40 mg PO BID pantoprazole for 30 days. Supportive treatment, ICU stay, and repeat EGD were per ICU guidelines. Patients were treated for *H. pylori* infection if positive, using standard regimens determined by the admitting physician.

Patients continued to receive 40 mg PO BID of pantoprazole for at least 30 days after the initial PO or IV treatment. During this period the patients followed up with their primary care physicians, who made the decision whether to continue this therapy beyond 30 days. Rebleeding as an outpatient was defined as visible bleeding in the form of melena or hematemesis. The patient's clinical status was monitored after discharge by telephone conversation.

The primary end point was rebleeding within 30 days of the index NVGIB (defined as vomiting of fresh/altered blood or melena with a drop in hemoglobin of 2 g/dl). Secondary end points were (a) duration of hospitalization; (b) number of blood transfusions; (c) new end-organ dysfunction within 30 days of admission considered secondary to NVGIB (defined as new-onset cardiovascular [angina, myocardial infarction or congestive heart failure], renal [prerenal azotemia secondary to GI bleed-induced hypovolemia, defined as new rise in serum creatinine $>$3 mg/dl and serum BUN/creatinine ratio $>$20], hepatic [ischemic hepatitis with ALT and AST $>$500 IU/L], neurologic [watershed brain infarcts on CT], or colonic [ischemic colitis diagnosed by colonoscopy and biopsy] dysfunction); and (d) mortality within 30 days of admission.

Results

A total of 25 patients were studied. Thirteen were randomized to the IV arm and 12 to the PO arm. During the recruitment period, no patient was excluded secondary to inability to swallow.

There was no significant difference between the groups in the age and gender distribution, smoking, or the use of alcohol, NSAIDs, anticoagulants, or antiplatelet drugs in the month prior to admission. Mode of presentation, hemodynamic variables, hematocrit,and INR on admission were also similar across the arms. Rockall and comorbidity scores also showed no significant difference between the groups (Table 1).

There were no significant differences in the sources of the NVGIB between the two groups. The endoscopic characteristics and interventions performed are shown in Table 2.

There was no significant difference in the proportion of patients found to be infected with *H. pylori* (IV group, 6 of 13, vs. PO group, 6 of 12).

Primary and secondary end points

None of the patients in the oral group rebled or developed any other secondary end points such as end-organ failure or

Table 1 Demographic and presentation characteristics

	IV ($N = 13$)	PO ($N = 12$)	P value
Age	66.2 ± 6.2	59.5 ± 19.4	0.36
Gender (M/F)	10/3	6/7	0.22
Alcohol use	56%	42%	0.08
Smoking	46%	33%	0.08
Prior medication (NSAID, anticoagulant, antiplatelet drug)	95%	100%	1.00
Pulse on admission	90.8 ± 17.9	91.8 ± 17.6	0.89
Systolic BP on admission	125.1 ± 32.6	106.8 ± 23.0	0.12
Mode of presentation: melena/hematemesis/hematochezia	11/2/0	10/1/1	
Hematocrit on admission	25.7 ± 7.6	24.86 ± 8.6	0.8
INR on admission	1.42 ± 1.05	1.14 ± 0.24	0.38
Rockall score	5.3 ± 2.5	4.5 ± 2.1	0.39
Comorbidity score	3.3 ± 2.6	2.2 ± 1.9	0.28

death. One patient in the IV group rebled within 30 hr of his index NVGIB. This patient was found to have a duodenal ulcer with an adherent clot at the index EGD, which was treated with epinephrine injection alone. During the second EGD an actively spurting arterial vessel was noted in the duodenal ulcer, which was controlled with epinephrine injection, bipolar cautery, and endoclip placement. There was no further rebleeding at the end of 30-day follow-up in this patient. Another patient randomized to the IV group had evidence of rebleeding after 4 days of therapy initiation during which he had received IV pantoprazole infusion for 3 days and PO pantoprazole for 1 day per the study protocol. This particular patient had presented with a gastric ulcer with an adherent clot, which was removed, and the ulcer was treated with epinephrine injection and BICAP cautery. Repeat EGD showed active bleeding from the same ulcer and temporary control was achieved using epinephrine and bipolar cautery. However, the patient continued to bleed, requiring surgical intervention by day 6 of the index NVGIB. A third patient randomized to the IV group developed end-organ failure in the form of new-onset renal failure without evidence of rebleeding. This resolved within 1 week of admission.

Although two patients in the IV arm rebled and another one developed reversible renal failure, compared to none in the PO arm, these outcomes were not statistically significant ($P = 0.48$, Fisher exact test) (Table 3).

Subgroup analysis of the eight patients in the IV and eight patients in the PO arm who had ulcers with stigmata (adherent clot, visible vessel, active bleed, and red spot) did not show any significant difference in rebleeding rates ($P = 0.46$, Fisher exact test) or organ failure ($P = 0.99$).

There was no significant difference between the groups in the duration of hospitalization or number of blood transfusions used (Table 3).

None of the patients developed adverse effects to pantoprazole therapy. All patients were discharged home on a regimen of 40 mg PO pantoprazole BID and, on questioning by telephone 30 days after admission, claimed to be adherent to the prescribed dosage.

None of the PO group developed late complications and none of these patients had to be switched to the IV group.

Table 2 Ulcer stigmata and endoscopic interventions

	IV ($N = 13$)	PO ($N = 12$)
Ulcer location		
Duodenal	4	5
Gastric	5	5
Duodenal and gastric	2	1
Gastric and esophageal	1	1
Duodenal and esophageal	1	0
Ulcer stigmata		
Active bleeding	4	3
Visible vessel	4	3
Red spot	0	2
Clean base	5	4
Therapeutic intervention		
None	6	7
Epinephrine injection alone	1	0
Epinephrine + bipolar coagulation	5	3
Epinephrine + bipolar coagulation + endoclips	1	2

Note. P = not significant (Fisher exact test).

Table 3 Primary and secondary end points

	IV ($n = 13$)	PO ($n = 12$)	P value
Rebleeding	2 (15%)	0 (0%)	0.46
Organ failure	1 (8%)	0 (0%)	0.99
Mortality	0 (0%)	0 (0%)	
Blood transfusions (units)	3.9 ± 3.7	3.6 ± 2.4	0.813
Duration of hospitalization	6.8 ± 4.8	5.2 ± 3.3	0.34

There were no mortalities in either group at the end of 30 days.

Discussion

NVGIB continues to be a significant problem, requiring resuscitative and endoscopic therapy [1]. Rebleeding after initial control of bleeding is an important clinical issue, which can result in end-organ dysfunction and death [2]. Acid suppression, in the form of H_2 blockers and PPIs, has been shown to be of benefit in prevention of rebleeding, possibly because of improvement in platelet aggregation with increased gastric pH [4]. Recent meta-analyses have shown superiority of PPI compared to H_2 blockers in prevention of rebleeding after NVGIB. A study by Khuroo *et al*. compared placebo with 40 mg BID PO omeprazole in 220 patients with upper GI bleeding secondary to acid peptic disease [4]. They reported significantly decreased risk of rebleeding, need for surgical intervention to stop the bleeding, and transfusion requirements in patients receiving omeprazole compared to placebo. Mortality remained similar across the two groups. This trial was flawed because there was no endoscopic therapy provided to the patients. Lau *et al*. compared the effect of IV omeprazole with placebo in 240 patients with peptic ulcer bleeding after initial endoscopic therapy [5]. They were also able to demonstrate a decrease in the rate of rebleeding in patients given IV omeprazole compared to placebo. However, there was no significant improvement in rates of surgical intervention and mortality. IV omeprazole is not FDA approved for use in the United States.

Gastric pH has been used as a marker for the effectiveness of both PO and IV PPIs in several studies [8]. At the time of commencement of this study the only FDA-approved IV PPI in the United States was pantoprazole. The intragastric pH increase with PO pantoprazole is dose dependent and predictable [10]. A study comparing inhibition of gastric acid secretion of 40 mg PO pantoprazole with a similar IV dose showed that they are equipotent in raising the gastric pH [8]. Besides requiring nursing supervision, IV pantoprazole is more expensive than the orally administered form and requires a dedicated IV line in a patient who may need those lines for blood or crystalloid and colloid replenishment. With the background of similar potency of PO and IV pantoprazole in gastric acid suppression, we did a pilot study to determine the effectiveness of PO pantoprazole in the management of NVGIB.

The study results indicate that PO pantoprazole given at a dose of 80 mg BID for 3 days has a similar effect on rebleeding and end-organ failure compared to IV pantoprazole given as an 80-mg IV bolus and 8 mg/hr infusion for 3 days. All patients were then on PO pantoprazole, 40 mg BID, for at least 30 days.

The population included in the present study, despite the small numbers, is representative of the typical hospital admission for NVGIB, i.e., age >60 years, recent use of NSAIDs, anticoagulants, or antiplatelet agents, and multiple comorbid conditions [11, 12]. None of the patients randomized to the PO arm had to be switched to the IV mode of administration and no adverse effects of pantoprazole therapy were observed. Although two patients in the IV pantoprazole arm, as opposed to none in the PO pantoprazole arm, experienced rebleeding, a potential type I error because of small numbers cannot be excluded and hence larger-scale trials are needed to substantiate this preliminary finding. This being a pilot study, the number of patients was small. Since randomization was done before EGD, five patients in the IV and four patients in the PO group were found to have ulcers with a low likelihood of rebleeding (clean base) and did not require endoscopic intervention. However, the remaining eight patients in the IV and eight in the PO group were treated endoscopically in conjunction with their randomized route of pantoprazole administration and still showed no significant difference in rebleeding rate or other end points.

The Rockall score [9] and comorbidity score, which are well-validated measures of prognosis after NVGIB, were similar across the two groups. In accordance with previous studies, we did not find any significant difference in *H. pylori* positivity, blood transfusion rates, or duration of hospitalization between the PO and the IV pantoprazole groups.

Although we had no patients during the randomization who could not take PO pantoprazole, IV PPI would still be the optimal route for those patients who are unable to take oral medications.

Our pilot trial suggests that orally administered pantoprazole is a feasible, safe alternative to IV pantoprazole therapy in the prevention of rebleeding in patients with NVGIB. This study should form the basis for large-scale trials comparing these two modes of PPI administration for NVGIB.

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