Continuous Infusion of Pantoprazole with Octreotide Does Not Improve Management of Variceal Hemorrhage

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Study Objective. To assess the effect of a prolonged continuous infusion of pantoprazole on patient outcomes when the drug was combined with standard octreotide therapy in patients with variceal hemorrhage.

Design. Retrospective cohort study.

Setting. Large academic hospital.

Patients. One hundred thirty adults who received treatment for a documented variceal hemorrhage; 53 patients received standard octreotide therapy plus a prolonged continuous infusion of pantoprazole (continuous-infusion group) and 77 patients received either octreotide alone, octreotide with a short-term (< 24 hrs) infusion of pantoprazole, or octreotide with intermittent acid suppression (control group).

Measurements and Main Results. The primary outcome measure was the number of units of packed red blood cells transfused during hospitalization. Baseline characteristics between the treatment groups were similar. The duration of therapy for variceal hemorrhage was significantly longer in the continuous-infusion group than in the control group. Transfusion requirements for packed red blood cells (mean ± SD 6.4 ± 6.5 vs 5.8 ± 6.6 units, p=0.66) and platelets (8.8 ± 15.1 vs 5.1 ± 11.9 units, p=0.13) were similar for the continuous-infusion group versus the control group. The continuous-infusion group, however, received significantly more units of fresh-frozen plasma than the control group (6.1 ± 10.6 vs 2.9 ± 6.2 units, p=0.05). There was no significant difference in mortality rate between groups.

Conclusion. Prolonged continuous infusions of pantoprazole with octreotide seemed to offer no additional benefit compared with octreotide plus short-term infusions of pantoprazole or intermittent acid suppression in the management of acute variceal hemorrhage. Prospective studies should be conducted to evaluate the role of continuously infused proton pump inhibitors in this setting before their use can be advocated.

Key Words: pantoprazole, continuous infusion, varices, variceal hemorrhage, octreotide.

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Variceal hemorrhage is a major, life-threatening complication of gastroesophageal varices, which develop in approximately 50% of patients with cirrhosis.[1] The frequency of variceal rupture varies depending on the size of the varices, but is generally 5–15%/year. Despite improvements in treatment over the last decade, variceal hemorrhage is associated with a mortality rate of at least 20% after 6 weeks.[2, 3]

Recommendations for controlling active bleeding include starting pharmacologic therapy with somatostatin, its analogs, or terlipressin and continuing therapy for 3–5 days.[1] Octreotide is the somatostatin analog available in the United

States. When given as a continuous infusion, the agent has been associated with improved outcomes.[4] Octreotide decreases portal pressure by inducing splanchnic vasoconstriction, leading to control of bleeding.

Continuous infusions of proton pump inhibitors have been associated with a decreased risk for recurrent bleeding and a decreased need for endoscopic intervention in patients with bleeding peptic ulcers.[5, 6] Data support the use of omeprazole administered as an 80-mg bolus followed by a continuous infusion of 8 mg/hour for 72 hours to prevent recurrent ulcerous bleeding in high-risk patients. Although parenteral omeprazole is not available in the United States, parenteral pantoprazole has been recommended for use.[7]

Although data support the continuous infusion of a proton pump inhibitor in the setting of nonvariceal hemorrhage, to our knowledge, no research has been conducted to evaluate its use in patients with variceal hemorrhage. Thus, we investigated the potential benefit of administering pantoprazole as a prolonged continuous infusion combined with standard octreotide therapy compared with octreotide alone or octreotide with intermittent acid suppression or with short-term (< 24 hrs) continuous-infusion pantoprazole to manage bleeding varices.

Methods

This retrospective cohort study was conducted at a major academic medical center (University of Michigan Medical Center, Ann Arbor, MI). The study was approved by the University of Michigan's institutional review board. Patient consent was not required due to the noninterventional, retrospective nature of the study.

We reviewed the hospital's patient database to identify patients who had received continuous infusions of octreotide between January 2002 and June 2005. All patients who had a documented variceal hemorrhage, as determined by esophagogastroduodenoscopy, were included. The null hypothesis was that continuous infusions of pantoprazole therapy for longer than 24 hours reduced variceal bleeding. Therefore, we assigned patients to one of two groups: a continuous-infusion group and a control group. The continuous-infusion group consisted of patients who had received continuously infused pantoprazole for at least 24 hours in addition to standard octreotide therapy. The control group was composed of patients who had received either octreotide alone, octreotide with pantoprazole that was continuously infused for less than 24 hours, or octreotide with intermittent acid suppression. Because the source of hemorrhage is not known at presentation, we allowed patients in the control group to have received empiric infusions of pantoprazole, a practice that consensus guidelines support.[7]

Demographic data were collected, including age, race-ethnicity, sex, Child-Pugh score, and Acute Physiology and Chronic Health Evaluation (APACHE) III scores, if available. Relevant medical histories were documented and included a history of transjugular intrahepatic portosystemic shunt procedures, number of variceal bleeding episodes, previous use of β-blockers, and duration of cirrhosis. Laboratory data were collected at baseline and end of therapy, including hemoglobin level and hematocrit; albumin, bilirubin, blood urea nitrogen, and serum creatinine concentrations; and activated partial thromboplastin times (aPTTs) and international normalized ratios (INRs). Dosages and durations of pantoprazole given as both intermittent injections and continuous infusions and octreotide given as continuous infusions were recorded. Other acid-suppressive therapy was also recorded.

The primary outcome measure was the number of units of packed red blood cells transfused during the patient's hospitalization. Secondary outcome measures included the number of units of fresh frozen plasma, platelets, and cryoprecipitate transfused; endoscopic interventions;

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Table 1. Baseline Characteristics

Characteristic	Continuous-Infusion Group[a] (n=53)	Control Group[b] (n=77)	p Value
	No. (%) of Patients		
Caucasian	43 (81)	56 (73)	NR
Male	37 (70)	53 (69)	0.94
Previous variceal bleeding	23 (43)	44 (57)	0.086
Previous β-blocker therapy	16 (30)	35 (45)	0.058
Gastric varices	16 (30)	21 (27)	0.84
	Mean ± SD		
Age (yrs)	52.0 ± 11.2	52.1 ± 11.8	0.99
Albumin level (g/dl)	2.2 ± 0.7	2.4 ± 0.7	0.07
Bilirubin level (mg/dl)	5.0 ± 7.1	3.4 ± 5.7	0.15
aPTT (sec)	37.3 ± 15.2	33.5 ± 11.1	0.10
INR	1.6 ± 0.6	1.5 ± 0.6	0.31
Hemoglobin level (g/dl)	9.1 ± 2.2	9.1 ± 2.5	0.96
Hematocrit (%)	27.3 ± 6.2	27.0 ± 6.9	0.83
Child-Pugh score	9.9 ± 2.4	9.4 ± 2.1	0.21
APACHE III score[c]	83.8 ± 21.7	85.2 ± 39.3	0.85
Duration of infusion (hrs)			
Octreotide	70.9 ± 33.2	48.4 ± 31.9	0.0001
Pantoprazole	63.3 ± 48.9	3.5 ± 6.8	<0.001

NR = not reported; aPTT = activated partial thromboplastin time; INR = international normalized ratio; APACHE = Acute Physiology and Chronic Health Evaluation.
[a]Patients received standard octreotide therapy plus a prolonged continuous infusion of pantoprazole.
[b]Patients received either octreotide alone, octreotide with a short-term (< 24 hrs) infusion of pantoprazole, or octreotide with intermittent acid suppression.
[c]Data were available for 32 patients in the continuous-infusion group and 40 patients in the control group.

frequency of rebleeding; length of stay in the intensive care unit; length of hospitalization; and mortality rate. Episodes of rebleeding were based on repeated use of blood transfusions after initial stabilization, repeated endoscopy, or repeated transjugular intrahepatic portosystemic shunting.

Statistical Analysis

To prove the null hypothesis, the continuous-infusion group and the control group were compared for baseline characteristics, duration of drug infusions, endoscopic interventions and clinical outcomes, and number of transfusions received. The Student *t* test was used to compare continuous variables, and the Fisher exact test or χ^2 test was used to compare categoric data. A p value of 0.05 or less was considered to indicate a statistically significant difference.

Results

Demographic and Treatment Data

Of 336 patients screened, 130 met the criteria for inclusion. The 206 patients excluded had received octreotide for reasons other than variceal bleeding (180 patients), or they had an incomplete inpatient record (26 patients). Of the 130 patients in the study, 53 were in the continuous-infusion group. Of the 77 in the control group, three received octreotide alone, 24 were given octreotide with a short-term infusion of pantoprazole, and 50 received octreotide with intermittent acid suppression. Acid suppressive therapy consisted of intravenous pantoprazole twice/day in 48 patients and intravenous ranitidine 3 times/day in two patients.

Baseline characteristics were similar between treatment groups (Table 1). More patients in the control group than in the continuous-infusion group had a history of variceal bleeding (57% vs 43%, p=0.086) and previous β-blocker therapy (45% vs 30%, p=0.058). In addition, mean ± SD albumin levels tended to be higher (2.4 ± 0.7 vs 2.2 ± 0.7 g/dl, p=0.07) and bilirubin levels tended to be lower (3.4 ± 5.7 vs 5.0 ± 7.1 mg/dl, p=0.15) in the control group than in the continuous-infusion group. Measures of coagulopathy (INR and aPTT) were similar between groups, as were mean ± SD Child-Pugh scores (control 9.4 ± 2.1

Table 2. Study Interventions and Outcomes

Variable	Continuous-Infusion Group[a] (n=53)	Control Group[b] (n=77)	p Value[c]
Transfusions (units)			
Day 1			
Packed red blood cells			
Mean ± SD	3.0 ± 3.0	2.9 ± 3.2	0.85
Median	2	2	
Fresh-frozen plasma			
Mean ± SD	1.7 ± 2.6	1.0 ± 1.8	0.07
Median	0	0	
Platelets			
Mean ± SD	2.1 ± 3.7	1.3 ± 3.9	0.24
Median	0	0	
Throughout hospital stay			
Packed red blood cells			
Mean ± SD	6.4 ± 6.5	5.8 ± 6.6	0.66
Median	4	4	
Fresh-frozen plasma			
Mean ± SD	6.1 ± 10.6	2.9 ± 6.2	0.05
Median	2	0.5	
Platelets			
Mean ± SD	8.8 ± 15.1	5.1 ± 11.9	0.13
Median	0	0	
Laboratory value at end of therapy, mean ± SD			
Hemoglobin level (g/dl)	10.7 ± 1.5	10.7 ± 1.5	0.9
Hematocrit (%)	30.7 ± 4.6	31.1 ± 4.8	0.65
Clinical outcomes, no. (%) of patients			
Recurrent variceal bleed	7 (13)	4 (5)	0.12
Mortality	7 (13)	13 (17)	0.63
Endoscopic interventions, no. (%) of patients			
Banding	22 (42)	31 (40)	0.89
Sclerotherapy	19 (36)	23 (30)	0.47
TIPS	18 (34)	24 (31)	0.74

TIPS = transjugular intrahepatic portosystemic shunting.
[a]Patients received standard octreotide therapy plus a prolonged continuous infusion of pantoprazole.
[b]Patients received either octreotide alone, octreotide with a short-term (< 24 hrs) infusion of pantoprazole, or octreotide with intermittent acid suppression.
[c]Student *t* test was used to compare all variables all except clinical outcomes and endoscopic interventions, for which the χ^2 test was used.

vs continuous infusion 9.9 ± 2.4, p=0.21) and APACHE III scores (control 85.2 ± 39.3 vs continuous infusion 83.8 ± 21.7, p=0.85).

Octreotide was infused for a mean ± SD of 48.4 ± 31.9 hours (range 1.5–173 hrs) in the control group compared with 70.9 ± 33.2 hours (range 8–149 hrs) in the continuous-infusion group (p=0.0001). Doses of octreotide were 47.1 ± 11.9 and 46.0 ± 9.1 µg/hour in the control and continuous-infusion groups, respectively (p=0.6). Pantoprazole was infused for 3.5 ± 6.8 hours (range 0–22 hrs) in the control group compared with 63.3 ± 48.9 hours (range 25–332 hrs) for continuous infusion (p<0.001). The dosage of pantoprazole used for continuous infusion was 8 mg/hour for 52 of 53 patients in the continuous-infusion group and for 22 of 24 patients in the control group.

Seventy-two (94%) patients in the control group received a proton pump inhibitor (as a continuous infusion for < 24 hrs and/or intermittent injections). Fifty patients (94%) in the continuous-infusion group received intermittent therapy with a proton pump inhibitor after their continuous infusions of pantoprazole were discontinued.

Outcome Measures

Mean numbers of packed red blood cell and platelet transfusions on day 1 of variceal hemorrhage and throughout hospitalization were similar between the study groups (Table 2). During hospitalization for the control and continuous-infusion groups, total mean ± SD packed red blood cells transfused were 5.8 ± 6.6 and 6.4 ± 6.5 units, respectively (p=0.66), and total platelet transfusions were 5.1 ± 11.9 and 8.8 ± 15.1 units, respectively (p=0.13). Patients given continuous infusions received more fresh frozen plasma than did control patients (total 6.1 ± 10.6 vs 2.9 ± 6.2 units, p=0.05).

At the end of therapy, the control and continuous-infusion groups had similar mean ± SD serum hemoglobin concentrations (10.7 ± 1.5 vs 10.7 ± 1.5 g/dl, p=0.9) and hematocrits (31.1 ± 4.8% vs 30.7 ± 4.6%, p=0.65; Table 2). Four (5%) control patients had a recurrence of variceal hemorrhage compared with seven (13%) in the continuous-infusion group (p=0.12). We found no significant difference between the groups with respect to variceal banding, sclerotherapy, or transjugular intrahepatic portosystemic shunt placement. Mortality rates were similar, with 13 (17%) deaths in the control group and seven (13%) deaths in the continuous-infusion group, p=0.63.

Subgroup Analyses

Of 53 patients who received a continuous infusion of pantoprazole for at least 24 hours, 16 received therapy for more than 72 hours (mean ± SD 108.7 ± 64.3 hrs). Also, the octreotide infusion was significantly longer in this subgroup than in the control group (92.4 ± 32.7 vs 48.4 ± 31.9 hrs, p<0.001). At baseline, for this subgroup, serum hemoglobin levels, aPTTs, and INRs did not significantly differ from the control group. Also similar between this subgroup and the control group were the mean ± SD number of packed red blood cells transfused on day 1 (2.5 ± 1.9 vs 3.0 ± 3.4 units, p=0.64) and the total number of packed red blood cells transfused (5.9 ± 6.9 vs 5.8 ± 6.8 units, p=0.96).

Sixteen patients in the continuous-infusion group and 21 control patients presented with bleeding from gastric varices. Evaluation of these patients showed no significant difference in units of packed red blood cells transfused (continuous infusion 6.0 units vs control 4.8 units, p=0.48). Pantoprazole infusions were significantly longer in this continuous-infusion group (mean ± SD 63.3 ± 30.7 hrs) than in this control group (3.7 ± 7.3 hrs, p<0.001). Overall, octreotide infusions were longer for these 16 patients receiving continuous infusions (72.0 ± 31.6 hrs) than for the 21 control patients (46.6 ± 41.8 hrs, p=0.04).

Discussion

The estimated overall incidence of acute upper gastrointestinal bleeding is 50–100 episodes/100,000 person-years, with an annual hospitalization rate of 100/100,000 hospital admissions.[8] The most common cause of such hemorrhage is ulcerative disease. National surveys have shown that approximately 10% of patients with upper gastrointestinal bleeding present with variceal hemorrhage,[9, 10] but this rate may be as high as 30% in large urban areas.[11] The general recommendation is to start therapy with a proton pump inhibitor in patients who are being evaluated for upper gastrointestinal bleeding.[7]

In our study, to account for the intent of pantoprazole use, we assigned all patients who had pantoprazole continuously infused for less than 24 hours to the control group. The assumption was that these patients might have received empiric therapy before undergoing esophagogastroduodenoscopy and that their infusions were stopped when variceal bleeding was diagnosed. About 69% of patients in this group did not receive continuously infused pantoprazole. Although the mean duration of pantoprazole infusion in the continuous-infusion group was not 72 hours, as it is prescribed for nonvariceal bleeding, it was significantly longer than the mean duration in the control group.

Despite the prolonged infusion of pantoprazole, we observed no added benefit with respect to transfusion requirements. The mean number of transfusions for both the continuous-infusion group (6.4 units) and the control group (5.8 units) was somewhat higher than those reported in previous prospective studies.[4, 12, 13] Two aspects of our patient population may account for the difference. First, our patients' mean hemoglobin concentration after therapy (10.7 g/dl in both groups) was higher than hemoglobin goals in previous studies (9 g/dl,[4] 8 g/dl,[13] and > 7 g/dl[12]). Second, Child-Pugh class C disease was more prevalent in our patients (44.6%) than in patients from previous studies (36.7%,[4] 14.8%[13] and 11.8%[12]).

Despite recommendations that octreotide infusions should last 3–5 days,[1] the mean duration of therapy in our control group was

48.4 hours compared with 70.9 hours in the continuous-infusion group. It is difficult to account for this discrepancy, as baseline characteristics, endoscopic interventions, and responses to therapy suggested that the treatment groups were similar. Continuous infusion of pantoprazole in the setting of upper gastrointestinal bleeding is a relatively recent practice, a fact reflected in the patient groups. That is, most of the patients treated last were in the continuous-infusion group. Thus, the prolonged administration of octreotide in the continuous-infusion group may have simply reflected an evolution in practice. Although it may be argued that this difference provided an additional benefit to the continuous-infusion group, significant controversy surrounds both the relative efficacy of octreotide and the time frame in which it exerts its effect.

A review of existing data suggested that the net benefit of octreotide is that it saves 0.5 unit of blood/patient.[14] In addition, desensitization[15] to the effects of octreotide in patients with portal hypertension implies a limited duration of efficacy,[16] an observation made previously.[4] Therefore, although our two treatment groups received octreotide for different durations, we do not believe that this difference affected patient outcomes.

The use of a proton pump inhibitor in the setting of a bleeding peptic ulcer after endoscopic intervention has been shown to decrease the number of blood transfusions and the frequency of rebleeding in high-risk patients.[5] The presumed mechanism is maintenance of the gastric pH above 6 to optimize platelet aggregation and subsequent clot formation.[17, 18]

Our study did not demonstrate a beneficial effect of continuously infused pantoprazole on either the requirements for blood transfusion or the frequency of rebleeding. Also, our subset analysis of patients who received continuous infusions of pantoprazole for at least 72 hours revealed no benefit in outcomes measures. Most bleeding episodes were due to esophageal varices rather than gastric varices. Therefore, the potential gain of achieving clinically significant acid suppression in this patient population with esophageal varices seems unlikely. Because proton pump inhibitors have demonstrated improvements in actively bleeding peptic ulcers, patients presenting with bleeding gastric varices may benefit from continuously infused pantoprazole. Subset analyses of patients presenting with gastric variceal hemorrhage did not reveal any advantage with infusions of pantoprazole.

The retrospective nature of this study was one of its limitations. Furthermore, the duration of infusions varied widely within the treatment groups, though the mean durations did differ significantly. Although the APACHE III scores that were available were similar between the groups, the continuous-infusion group received more fresh-frozen plasma, they received longer infusions of octreotide, and they tended to have more recurrent bleeding than the control group. These differences suggested that the groups might not have been equal at baseline. It is also possible that intensified therapy may have been related to changes in practice over time.

Conclusion

The findings of our study did not reveal any benefit of prolonged continuous infusions of pantoprazole compared with short-term (< 24 hrs) infusions or intermittent dosing when it was combined with octreotide in the management of variceal hemorrhage. Prospective studies should be conducted to evaluate the role of continuously infused proton pump inhibitors in this setting before their use can be advocated.

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