Proton Pump Inhibitors After Endoscopic Hemostasis in Patients With Peptic Ulcer Bleeding

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SUMMARY
Background: Peptic ulcer bleeding is a common and potentially fatal condition. For patients with bleeding peptic ulcers that display major endoscopic stigmata of recent hemorrhage, a combination of endoscopic and pharmacologic therapy is the current standard management. Objective: To show our experience with management of peptic ulcer bleeding. Patients: Patients who presented with gastrointestinal hemorrhage caused by peptic ulcer or recent history (<24 h before presentation) of hematemesis and/or melena admitted to our hospital emergency departments, and patients whose ulcer hemorrhage started after hospitalization for an unrelated medical or surgical condition. Methods: Patients with actively bleeding ulcers and those with nonbleeding visible vessel or adherent clot were treated with epinephrine injection and/or endoscopic hemoclip, and randomized to receive intravenous pantoprazole according to the continuous regimen (dose of 5 x 40 mg in continuous infusion of 8 mg/h for 72 h) or the standard regimen (40 mg bolus of PPI twice daily for 3 days). After the infusion, all patients were given 40 mg PPI twice daily orally. The primary end point was the in-hospital rebleeding rate, as discovered by the repeated endoscopy. Results: Bleeding recurred in 5 of 34 patients (14.7%) receiving the intensive regimen group was 93.5 ± 23.8, and in intensive regimen group 106.6 ± 22.4 (P = 0.042). Mean units of blood transfusion needed for the prevention of ulcer rebleeding, should be considered for treatment failures. The choice between surgery and repeat endoscopic therapy should be based on the pre-existing co-morbidities of the patient and the characteristics of the ulcer (1).

1. INTRODUCTION
Peptic ulcer bleeding is a common and potentially fatal condition. It is best managed using a multidisciplinary approach by a team with medical, endoscopic and surgical expertise. The management of peptic ulcer bleeding has been revolutionized in the past two decades with the advent of effective endoscopic hemostasis and potent acid-suppressing agents. A prompt initial clinical and endoscopic assessment should allow patients to be triaged effectively into those who require active therapy, versus those who require monitoring and preventative therapy. A combination of pharmacologic and endoscopic therapy (using a combination of injection and endoscopic hemoclip) offers the best chance of hemostasis for those with active bleeding ulcers. Surgery, being the most effective way to control bleeding, should be considered for treatment failures. The choice between surgery and repeat endoscopic therapy should be based on the pre-existing co-morbidities of the patient and the characteristics of the ulcer (1). In patients with upper gastrointestinal bleeding caused by peptic ulcer disease, intravenous proton-pump-inhibitor therapy seems to be beneficial. Following successful endoscopic hemostasis, Lau et al. (2), demonstrated that the use of intravenous IPP 40 mg every 12 h reduced the rebleeding rate from 22.5% to 6.7%, this increase in frequency seemed to decrease the volume of blood transfusion needed. After 3 days of intravenous IPP treatment, the patient can be switched to daily 20 mg by mouth for 8 weeks (2). Therapy can be stopped after 8 weeks unless the patient has an associated Helicobacter pylori infection, is maintained on low-dose aspirin, or uses a nonselective NSAID. Patients with H. pylori infection are at higher risk of rebleeding and should receive a 14-day course of antibiotics in addition to proton-pump inhibitors (2, 3). Patients taking low-dose aspirin or nonselective NSAIDs are at high risk from the development of recurrent ulcers and should receive proton-pump-inhibitor maintenance therapy (4, 5). Patients who are H. pylori-negative, NSAID-negative, and have an idiopathic bleeding ulcer may not require any further therapy after the 8-week course of therapy is completed. Clearly, the best approach to this group of patients has yet to be determined.

2. METHODS
A randomized, study of PPI therapy for the prevention of ulcer rebleeding in high-risk patients after endoscopic hemostasis was conducted in Clinical centre, University of Sarajevo, Department of gastroenterology and hepatology on a nonprofit, voluntary basis. All study subjects were enrolled between January and December 2008.

3. PATIENT POPULATION
Patients who presented with gastrointestinal bleeding or a recent history (<24 h before presentation) of hematemesis and/or melena to our hospital emergency departments, and patients whose ulcer hemorrhage started after hospitalization for an unrelated medical or surgical condition were included, as were patients whose ulcer hemorrhage started after hospitalization for an unrelated medical or surgical condi-
tion. The reference time was the onset of symptoms and signs, or when bleeding started if the patient was already in hospital for other reasons.

Eligible patients were required to have an ulcer with either active bleeding (spurring arterial or persistent oozing) or a nonbleeding lesion (nonbleeding visible vessel or adherent clot) at endoscopy. According to Rockall’s criteria (17), patients determined to be at high clinical risk for rebleeding clinically were those with a Rockall score ≥6, calculated on patients’ demographic and clinical characteristics or volume and rapidity of blood loss: age ≥70 yr; concomitant illness, defined as a medical history of chronic illness or presence of acute medical condition; transfusion of ≥2 units of packed blood cells or hemoglobin ≤100 g/L; and hemodynamic instability, defined either by hypotension (systolic blood pressure ≤90 mmHg) or tachycardia (heart rate ≥100 beats per min). Hemodynamically unstable patients were initially resuscitated and then considered for enrolment if their condition stabilized. Exclusion criteria were malignant-appearing ulcers, severe comorbid conditions, oesophageal varices, severe coagulopathy (platelet count <100,000), need for continuous antiocoagulation, angioidplastic lesions.

4. ENDOSCOPIC HEMOSTASIS

The modality of endoscopic hemostasis, whether the epinephrine injection (1:10,000 dilution in saline, 1–1.5 cc/injection) was administered as monotherapy (unimodal) or in association with either mechanical therapy (multimodal), was at the discretion of the treating endoscopist. Hemostasis was considered to be established if bleeding had stopped. Clots covering ulcer lesions were washed by a water pump, and underlying nonbleeding visible vessels or adherent clots received endoscopic treatment. Patients with unsuccessful endoscopic hemostasis were not randomized.

5. SCHEDULE OF INTRAVENOUS IPPS

Individual investigators were allowed to use either pantoprazole or omeprazole. The choice was independent of preference, and was based on the costs at the pharmacy department of the local hospital. After randomization, the attending nurse prepared the locally available IPP (only pantoprazole) and started an infusion of the continuous regimen (dose of 5 x 40 mg in continuous infusion of 8 mg/h for 72 h) or the standard regimen (40 mg bolus of PPI twice daily, for 3 days). Patients were then transferred to a gastroenterology ward for monitoring and continuation of therapy.

After the initial 72 h, patients were switched to oral IPP ( pantoprazole or omeprazole) therapy (40 mg twice daily orally) until discharge. A repeat endoscopy was selectively used in high-risk patients, as determined by a Rockall score ≥6 at admission, but was mandatory in all patients with a suspected rebleeding. Patients in the low-risk group (Rockall score <6) were offered early resumption of feeding and monitored clinically.

6. OUTCOMES

The primary end point was the hospital occurrence of rebleeding, diagnosed at a repeat endoscopy. Patients clinically suspected of rebleeding were those who after an initial stabilization presented with at least one of the following signs: decrease in blood pressure (≤100 mmHg), increase in pulse rate (≥100 beats per min), decline in hemoglobin (≥20 g/L), no change in hemoglobin levels with red blood cell transfusions, or reappearance of overt bleeding (new hematemesis or melena). Patients with a clinical suspicion of rebleeding underwent a second attempt at endoscopic hemostasis: rebleeding was diagnosed if the ulcer was actively bleeding or if there was fresh blood in the stomach. Secondary outcomes included the need for surgery, transfusion requirement, length of hospital stay, and mortality.

7. STATISTICAL ANALYSIS

All patients who took at least one dose of drugs were included into the analysis. Categorical data were expressed as proportions (%), and continuous data as means ± standard deviation (SD).

For P values, the two-sample t-test was used for continuous variables and the Fisher exact test used for discrete variables.

A prediction model for rebleeding was developed including the following covariates: Rockall score (≥ or <6), type of PPI administered, PPI administration strategy (standard or intensive regimen), modality of endoscopic therapy (unimodal or multimodal), type of the index bleeding (whether active or inactive), and use of aspirin or nonsteroidal, anti-inflammatory drugs.

8. RESULTS

A total of 69 patients underwent randomization. The treatment groups were similar with respect to patients demographics, clinical characteristics, endoscopic modality, and PPI therapy (Table 1): two-thirds of patients were men, about 20% were older than 70 yr, and one third had taken aspirin or non-
steroidal anti-inflammatory drugs before hospitalization. Tree and five patients in the intensive and standard regimen groups, respectively, presented with a severe comorbidity. Signs of hemodynamic instability were more frequent in the standard regimen: shock was more common, mean Rockall score higher, and more patients had a Rockall score ≥6, and more patients had a Rockall score >6 versus <6.

The mean (±SD) number of units of blood transfused for all patients was 71.8 ± 45.8 in the intensive regimen group and 45.3 ± 50.2 in the standard regimen group (P = 0.026). Among patients with active bleeding, the mean hospital stay for 34 patients in the intensive regimen group was 5.8 ± 2.8 days, as compared with 6.4 ± 2.8 days for 35 patients in the standard group (P = 0.40).

One patient in died during the hospital stay; the cause of death was not linked to the bleeding event.

### 9. DISCUSSION

In patients with ulcer bleeding successfully treated at endoscopy, we found no evidence that an intensive dose PPI regimen reduced rebleeding compared with a less-intensive regimen of bolus injections: bleeding recurred in 14.7% and 22.8% of patients, respectively. The statistically equal rebleeding rate between the two intravenous IPP strategies is of relevance considering that patients treated with bolus IPPs presented more frequently with shock and signs of hemodynamic instability, two predictors of worse outcome (16, 20).

However, in patients who underwent simultaneous endoscopic hemostasis, two trials reported opposite results with the intensive IPP dosing versus placebo (11, 12), a single report showed a benefit of high-dose IPP therapy in comparison to H2R antagonists (25, 26), and four studies did not show a significant difference between an intensive regimen and standard bolus IPP injections.[13-16]

As intravenous IPP therapy is expensive, to be cost-effective the extra cost of the medication must be offset by a reduction in the occurrence of important adverse clinical outcomes.

In our study, patients who received the standard IPP regimen had advantages with respect to transfusion requirement, and rate of hemoglobin, but no advantage on need for surgery, length of hospital stay, or death rate. Moreover, cost-effectiveness analyses have yielded contrasting results regarding which of the two IPPs administration strategies is more effective in patients who have received concomitant endoscopic treatment.
data indicate a class effect of IPP therapy as inhibitors of gastric secretion; however, it is not always clear whether subtle variations in the pharmacokinetics and pharmacodynamics of individual IPPs are necessarily of clinical importance (32). Indeed, a similar rate of rebleeding has been found in a head-to-head comparative trial of omeprazole versus pantoprazole (32). As for the claim of a better outcome after dual endoscopic therapies as opposed to monotherapy with epinephrine injection (34,35), published data are not consistent. To the ongoing debate, we add our finding of similar rebleeding rates after hemostasis being achieved with either mono- or dual-endoscopic treatment. Furthermore, it has been shown that H. pylori-infected patients may respond differently to IPPs therapy than noninfected patients (36), but this information could be retrieved only for a third of enrolled patients in our study, therefore precluding the evaluation of its impact on the therapeutic outcomes of the study. A final shortcoming might be reporting only in-hospital events and excluding data on 30-day outcomes. Considering the mean duration of hospital stay of our patients, we feel confident the number of missed negative outcomes was very low.

**In conclusion**, in patients with bleeding peptic ulcers with successful endoscopic hemostasis the standard IPP regimen had advantage on transfusion requirements, but no advantage with respect to in-hospital rates of rebleeding rates, need for surgery, length of hospital stay, or death, what agrees with most recent studies (37).

**REFERENCES**

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