Does Adding Somatostatin to Proton Pump Inhibitor Improve the Outcome of Peptic Ulcer Bleeding?

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Background: Somatostatin has been shown to offer a distinct advantage over antisecretory drugs in the management of peptic ulcer bleeding (PUB). However, rebleeding rates are still high in spite of endoscopic and medical treatment. In this study, we intended to determine whether combined therapy of a proton pump inhibitor (PPI) plus somatostatin is more beneficial than a PPI alone in patients with PUB.

Methods: We enrolled 90 consecutive patients who presented with PUB between January 2006 and October 2007. All the patients were managed with endoscopic hemostasis and divided into two treatment groups: 1) PPI alone (group A) and 2) PPI plus somatostatin (group B). The primary outcome was rebleeding within 72 hours. The secondary outcomes were rebleeding in 30 days, packed red blood cells (pRBC) transfused, length of hospital stay, need for surgery, and in-hospital mortality.

Results: Forty-five patients in the PPI group (A) and 45 patients in the PPI plus somatostatin group (B) were studied. There was no difference between the two groups with respect to clinical and endoscopic features at admission. After medical treatment, there was no difference between groups A and B in rebleeding at 72 hours (11% vs. 13%, $p = \text{NS}$), rebleeding in 30 days (13% vs. 16%, $p = \text{NS}$), pRBC transfused (mean, 3.2 vs. 4.5 units, $p = \text{NS}$), length of hospital stay (mean, 7.4 vs. 8.4 days, $p = \text{NS}$), and in-hospital mortality (2% vs. 7%, $p = \text{NS}$).

Conclusions: Combined therapy with PPI and somatostatin did not result in better outcomes than PPI alone.

Key Words: hemorrhage, peptic ulcer, proton pump inhibitors, somatostatin.

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is a potentially life-threatening condition that often needs intensive care unit support.¹⁾ Among the causes of AUGIB, peptic ulcer is the most common, accounting for more than 50% of all cases.^{1,2)} The development of endoscopic therapies improved the outcomes of peptic ulcer bleeding.^{3,4)} However, the rebleeding rates and the mortality are still around 20% and 10%, respectively.⁵⁾ Thus, the role of medical therapy to stop bleeding or prevent recurrent bleeding would be important.

A stable blood clot in a peptic ulcer is crucial to maintain

hemostasis. Acidic gastric juice not only impairs clot formation, but also results in significantly greater clot lysis.⁶⁾ Therefore, maintenance of higher intragastric pH would be beneficial to reducing the risk of rebleeding. Proton pump inhibitors (PPIs) at high doses have been shown to reduce the risk of rebleeding in patients with peptic ulcer bleeding.⁷⁾ Compared to H₂-receptor antagonist or placebo, the use of intravenous PPIs is more effective in increasing intragastric pH and reducing rebleeding episodes.⁸⁻¹⁰⁾ Therefore, PPI is the gold standard of medical therapy in patients with peptic ulcer bleeding.

Somatostatin inhibits both acid and pepsin secretion and also reduces the mucosal blood flow of gastroduodenum.¹¹⁾ In some previous studies of peptic ulcer bleeding, somatostatin has been shown to be effective in bleeding control, transfusion reduction, and rebleeding prevention compared to H₂ antagonists or placebo.^{12,13)} A small pilot study showed that somatostatin was more effective than ranitidine and omeprazole in the prevention

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of recurrent hemorrhage following endoscopic injection therapy against bleeding peptic ulcers.¹⁴⁾ Therefore, we performed this study to investigate whether infusing the standard dose of somatostatin effects additional benefits to continuous infusion of high-dose PPIs in patients with peptic ulcer bleeding after endoscopic hemostasis.

MATERIALS AND METHODS

1) Patients

In this retrospective analysis, a total of 106 patients who were admitted to the Emergency Department at the Asan Medical Center in Korea with melena and/or hematemesis between January 2006 and October 2007 were considered for inclusion in this study. Patients who were older than 18 years and had gastroduodenal ulcers with spurting (Forrest Ia), oozing (Forrest Ib), or non-bleeding visible vessels (Forrest IIa), or adherent clots (Forrest IIb)¹⁵⁾ on endoscopy were eligible for the study. We excluded patients with a clean ulcer base, a malignant-looking ulcer, shock, or pregnancy. Therefore, a total of 90 patients were enrolled in the study.

2) Methods

All patients underwent endoscopic therapy within 8 hours after admission and a half of the patients were treated with intravenous (IV) pantoprazole (Altana Pharma AG, Konstanz, Germany) 80 mg bolus, followed by continuous infusion 8 mg/h in pantoprazole, which was designated as group 'A' and the other half in group 'B' were administered with IV pantoprazole as described above plus 48-hour infusion of somatostatin (Merck KGaA, Darmstadt, Germany) 250 μ g/h in normal saline after a bolus of 250 μ g. Follow-up endoscopy was performed every 48 hours until identification of a clean ulcer base. If a clean ulcer base was identified, continuous infusion of pantoprazole or/and somatostatin was switched to oral pantoprazole in both groups A and B, and patients were discharged out of hospital. Otherwise, only pantoprazole infusion was maintained in both groups until identification of a clean ulcer base. During hospitalization, the quantities of blood products transfused were monitored. After discharge, patients were followed up at a week interval. At every visit, history, BP, pulse rate, and hemoglobin levels were checked for monitoring of rebleeding. Coexisting illnesses were defined as cardiovascular diseases, renal failure, diabetes mellitus, and cancer.

Primary end point was rebleeding in 72 hours and secondary end points were as follows; rebleeding in 30 days, packed

RBC (pRBC) transfused, hospital stay, need for surgery, and in-hospital death. Rebleeding was defined as hematemesis or repeated melenas, or decrease in hemoglobin >2 g/dl, increase in pulse rate >100 beats per minute (bpm), or drop in systolic blood pressure <100 mmHg.

3) Statistics

Group comparisons were performed using the Student's *t*-test and χ^2 -tests. For all analyses, two-sided statistical tests were used. A *p*-value less than 0.05 was considered statistically significant. SPSS version 14.0 was used for all analyses.

RESULTS

Of the 90 patients, 69 (77%) patients were male and the median age was 63 years. As shown in Table 1, there was no significant difference between the PPI alone group and the PPI plus somatostatin group in clinical features. Overall, the endoscopic examination revealed gastric ulcer in 53 (59%) patients, duodenal ulcer in 31 (34%), and both in 6 (7%). Location and size of the ulcers were not different between two groups (Table 2). The initial endoscopic findings were similar between the two groups. Also as shown in Table 2, on endoscopic treatment, the amount of adrenaline injected, the use of clips or argon plasma coagulation were not different in both groups.

After endoscopic hemostasis, rebleeding in 72 hour was not significantly different between groups, as shown in Table 3. Similarly, there was no difference between two groups in rebleeding in 30 days, hospital stay, pRBC transfused, need for surgery, in-hospital death (Table 3).

No significant side effects were reported during the infusion

Table 1. Baseline Characteristics of Study Subjects

	PPI alone n = 45	PPI + SST n = 45	p value
Age (yr)*	60.2 $\pm$ 15.8	62.4 $\pm$ 15.2	NS
Gender (M/F), n	36/9	33/12	NS
History of ulcer, n (%)	9 (20%)	17 (37%)	NS
History of ulcer bleeding, n (%)	7 (16%)	12 (27%)	NS
Medical illness, n (%)	19 (42%)	20 (44%)	NS
Aspirin/NSAIDs, n (%)	19 (44%)	10 (24%)	NS
<i>Helicobacter pylori</i> infection, n (%)	16 (43%)	14 (40%)	NS
Systolic BP (mmHg)*	94.0 $\pm$ 28.3	96.2 $\pm$ 19.6	NS
Hemoglobin (g/dL)*	9.3 $\pm$ 2.7	9.2 $\pm$ 2.8	NS

PPI: proton pump inhibitor; SST: somatostatin; NS: not significant.

*: mean $\pm$ SD.

Table 2. Endoscopic Findings at Admission

	PPI alone n = 45	PPI + SST n = 45	p value
Location, n (%)			NS
Stomach	29 (64%)	24 (53%)	
Duodenum	13 (29%)	1 (40%)	
Both	3 (7%)	3 (7%)	
Size of ulcer, n (%)			NS
≤ 2 cm	34 (76%)	32 (71%)	
> 2 cm	11 (24%)	13 (29%)	
Bleeding signs, n (%)			NS
Spurting	4 (9%)	8 (18%)	
Oozing	6 (13%)	11 (24%)	
Non-bleeding visible vessel	26 (58%)	16 (36%)	
Adherent clot	9 (20%)	10 (22%)	
Dose of adrenaline (ml)*	4.9 ± 4.7	6.9 ± 5.2	NS
Endoscopic clips	13 (29%)	11 (24%)	NS
Argon plasma coagulation	13 (29%)	14 (31%)	NS

PPI: proton pump inhibitor; SST: somatostatin; NS: not significant.
*: mean ± SD.

period of somatostatin or PPIs in both groups and medication infusion was tolerable in both groups. During hospitalization, 4 patients (1 in group A and 3 in group B) died. Of them, one patient in group A and 2 in group B had recurrent bleeding and the other one in group B died of recurrent myocardial infarction.

DISCUSSION

In this study, we found that adding somatostatin to PPI treatment did not improve the clinical outcomes in patients with peptic ulcer bleeding. No major side effects were observed during treatment period and medication infusion was tolerable in both treatment groups.

Adoption of endoscopic hemostasis into the management of peptic ulcer bleeding has made a big improvement in outcomes of treatment. In a meta-analysis, endoscopic therapy significantly reduced the rates of rebleeding (odds ratio, 0.38; 95% confidence interval, 0.32–0.45), need for surgery (odds ratio, 0.36; 95% confidence interval, 0.28–0.45), and mortality (odds ratio, 0.55; 95% confidence interval, 0.40–0.76).³⁾ However, after endoscopic therapy, rebleeding still occurs in a substantial population. Hypotension, blood oozing, hemoglobin <10 g/dL, ulcer diameter >2 cm, and blood spurting were all independent predictors of rebleeding in a prospective study.¹⁶⁾ Accumulating evidence supports that intravenous PPI therapy may reduce rebleeding, need for surgery, and mortality. In a previous meta-analysis of 24 trials, treatment with PPIs had no

Table 3. Comparison of Clinical Outcomes between Two Treatment Groups

	PPI alone n = 45	PPI + SST n = 45	p value
Rebleeding in 72 h, n (%)	5 (11%)	6 (13%)	NS
Rebleeding in 30 d, n (%)	6 (13%)	7 (16%)	NS
Hospital stay (day)*	7.4 ± 5.2	8.4 ± 9.4	NS
pRBC (unit)*	3.2 ± 2.8	4.5 ± 4.4	NS
Surgery, n (%)	1 (2%)	0 (0%)	NS
In-hospital death, n (%)	1 (2%)	3 (7%)	NS

PPI: proton pump inhibitor; SST: somatostatin; NS: not significant.
*: mean ± SD.

significant effect on mortality (odds ratio, 1.01; 95% confidence interval, 0.74–1.40) but it resulted in significantly reduced rebleeding (odds ratio, 0.49; 95% confidence interval, 0.37–0.65), need for surgery (odds ratio, 0.61; 95% confidence interval, 0.48–0.78), and repeated endoscopic treatment (odds ratio, 0.32; 95% confidence interval, 0.20–0.51).¹⁰⁾ In a subgroup analysis, treatment with PPIs showed much lower death rates in patients with high risk stigmata, such as spurting or visible vessel, compared with placebo.¹⁷⁾ So far, many studies have been conducted to maximize the effects of PPIs on the outcomes of peptic ulcer bleeding. In a previous comparative study, high-dose omeprazole reduced the occurrence of rebleeding, need for surgery, and mortality in patients with high-risk peptic ulcer bleeding, as compared with standard-dose omeprazole. Another placebo-controlled randomized trial showed that preemptive infusion of omeprazole before endoscopy accelerated the resolution of signs of bleeding in ulcers and reduced the need for endoscopic therapy.¹⁸⁾

As mentioned above, somatostatin has the advantage of reducing the mucosal blood flow of gastroduodenum and pepsin secretion along with the inhibition of gastric acid. These effects may be of value in patients with peptic ulcer bleeding, especially the high-risk patients. However, the exact role of somatostatin in peptic ulcer bleeding has been still controversial. A previous study reported that somatostatin was more effective than pantoprazole in maintaining high intragastric pH,¹⁹⁾ where somatostatin was used at a dose of 500 ug/h, twice the dose given in our study. No serious adverse events have been reported in the previous report as well as our study.¹⁹⁾ It was suggested that the administration of 500 ug/h somatostatin as opposed to 250 ug may be more beneficial in reducing active bleeding in cirrhotic patients with upper gastrointestinal bleeding.²⁰⁾ The duration of vasoactive therapy when used as an adjuvant to endoscopic therapy has not yet been determined.

There is some evidence to suggest that patients presenting with a non-variceal upper gastrointestinal bleeding are at the highest risk of rebleeding in the first 3–5 days following initial hemostasis.^{21,22)} Therefore, 48-hour infusion of somatostatin cannot cover all the high-risk period of rebleeding.

Mortality occurred in 4 (4.4%) of the overall population. One of the 4 patients had myocardial infarction in the past history and died of recurrent myocardial infarction during hospitalization. Among the three who died of rebleeding, two showed spurting (Fla) on initial endoscopic examination. In addition, old age was associated with in-hospital death in our study. Three of the 4 patients had their age in 80's. Therefore, patients with older age and comorbid medical illnesses should be closely monitored during hospitalization.

In conclusion, combination of both medications did not show better outcomes and rebleeding rate was still high. To minimize the bleeding recurrence in the future, larger studies are needed to define the role of somatostatin in high-risk patients with peptic ulcer bleeding.

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