High- versus low-dose proton pump inhibitors post endoscopic hemostasis in hemodialysis cases with peptic ulcer bleeding

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Abstract

Post-endoscopic hemostasis treatment is not adequately addressed in high-risk patients on regular hemodialysis (HD) with emergency peptic ulcer bleeding. This study aimed to compare post-endoscopic high- versus low-dose proton pump inhibitors (PPIs) for peptic ulcer bleeding in patients undergoing regular HD.

This prospective study comprised 200 patients on regular hemodialysis having emergency peptic ulcer bleeding confirmed at endoscopy and managed with endoscopic hemostasis. Half of the patients received high-dose intensive regimen and the other half received the standard regimen. Patients who were suspected to have recurrent bleeding underwent a second endoscopy for bleeding control. The primary outcome measure was rate of recurrent bleeding during period of hospitalization that was detected through second endoscopy.

Rebleeding occurred in 32 patients ; 15 in the High-Dose Cohort and 17 in the Low-Dose Control (p = 0.700). No significant differences between the two dose cohorts regarding the time of rebleeding (p = 0.243), endoscopic hemostasis mode (p = 1.000), and need for surgery (p = 0.306). The high-dose regimen In-hospital mortality in high-dose group was 9.0% compared to 8.0% in the low-dose group (p = 0.800). Apart from the pre-hemostatic Forrest classification of ulcers, there were no significant differences between patients with re-bleeding ulcers (n=32) and those with non-rebleeding (n=168). Rebleeding was more common in class Ia, i.e. spurting bleeders (p < 0.001).

Endoscopic hemostasis followed by the standard low-dose PPI regimen of 40 mg daily IV boluses is safe and effective option for bleeding peptic ulcers in the high-risk patients under regular hemodialysis. (Acta gastroenterol. belg., **2021**, 84, **3-8**).

Keywords : Proton pump inhibitors, endoscopic hemostasis, hemodialysis patients, peptic ulcer bleeding.

Introduction

Bleeding from upper gastrointestinal (GI) tract is not uncommon clinical emergency that may present with life-threatening hemorrhage (1). The origin of bleeding can be variceal or non-variceal. Variceal bleeding is a detrimental adverse outcome of portal hypertension, that necessitates prompt and efficient management (2). On the other hand, The major contributor to non-variceal upper GI bleeding is peptic ulcer disease (3) ; it accounts roughly for 20-50% of cases in recent estimates (4,5). Gastrointestinal bleeding is a common complication of end-stage renal disease and is the reason for death in 3-7% of these cases (6-8). Gastroduodenal ulcers and erosions are common causes of upper GI bleeding in hemodialysis patients (9,10). This group of patients is at increased risk of upper GI bleeding due to several factors including high prevalence of arteriovenous malformations, associated co-morbidities, anemia (11,12), and exposure to clotting-modifying medications, especially when on regular hemodialysis (13).

The optimum management of emergency upper GI bleeding includes prompt resuscitation, risk stratification, pharmacologic and endoscopic intervention, and post-procedure therapy (14). Several previous clinical trials and meta-analyses have confirmed the significance of endoscopic hemostasis in the reduction of mortality, need for surgery, and ulcer rebleeding in high-risk patients (15-17). The beneficial effect of endoscopic hemostasis was confirmed in patients on maintenance hemodialysis with upper GI bleeding (18). However, the ideal post-endoscopic hemostasis treatment was not adequately addressed in literature.

Therefore, this study aimed to compare the use of high- and low-dose proton pump inhibitors (PPIs) following endoscopic control of bleeding peptic ulcers in patients undergoing regular hemodialysis regarding in-hospital rebleeding rate, need for surgical intervention, transfusion demands, period of hospitalization, and death.

Subjects and methods

This is a prospective observational non-randomized study that was made to assess the role PPI therapy in decreasing recurrent bleeding of peptic ulcer after endoscopic hemostasis in high-risk cases on regular hemodialysis. The current work was done in the period from May 2013 to December 2017. All eligible patients who presented within the study period were included in this study. The study protocol received approval by the local ethical committee. Written informed consents were given from all study subjects. The study included a consecutive sample of patients on regular hemodialysis who presented to the hospital emergency department with established bleeding from the gastrointestinal tract

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or a recent attack (within one day) of hematemesis and/or melena. Moreover, patients on regular hemodialysis who had ulcer hemorrhage that has begun after hospital admission for any other medical or surgical issues were enrolled in this study.

Inclusion criteria were patients on regular hemodialysis with an ulcer that showed either ongoing bleeding (jetting arterial or continuous trickling) or a nonbleeding lesion (nonbleeding detectable blood vessel or attached clot) at the time of endoscopic intervention. Hemodynamically unstable patients, at their initial presentation, were resuscitated at first and then considered for inclusion in the study if they became stable. Exclusion criteria were patients with malignant-looking ulcers or those with a flat spot or a clean base, patients with bleeding tendency (platelet count < 100,000 ; international normalized ratio > 1.5), or patients on antiplatelets or anticoagulants. Moreover, patients who were given PPI treatment prior to the index endoscopy were excluded from this study.

Endoscopic Hemostasis

The choice of the method of endoscopic bleeding control, whether the epinephrine bolus (1:10,000 dilution in saline, 1-1.5 mL/bolus) was used as monotherapy (unimodal) or in addition to either thermal (bipolar electrocoagulation or argon plasma coagulation) or mechanical (apposition of clips) therapy (multimodal), was done according to the estimate of the responsible endoscopist. Unimodal therapy with injection only was not the preferred choice (bimodal method was preferred).

Bleeding control was considered to be achieved if the bleeding had stopped. Endoscopic water pump was employed to wash clots that were covering ulcer lesions ; and then underlying nonbleeding detectable vessels or attached clots were managed endoscopically.

Schedule of Intravenous PPIs

Esomeprazole, omeprazole, or pantoprazole was used in the study. The selection was independent of researchers' predilection and was done according to the availability within the hospital. The study included 200 consecutive patients, the first one hundred patients were given an infusion of high-dose intensive approach (a loading dose of 80 mg on day 1, then constant infusion of 8 mg/h for 72 h). The second one hundred patients were given the standard approach (40 mg bolus of PPI twice daily). Cases were then carried to a gastroenterology section for observation and pursuit of treatment.

Oral PPI therapy (20 mg twice daily) was started after the initial 72 h, until patient discharge. Second endoscopy was individually employed in high-risk cases at admission, such as those presenting with shock but was obligatory in all cases with suspicion of rebleeding such as those with recurrence of hypotension or with hemoglobin drop. Approach of early start of feeding was adopted in the low-risk group.

Clinical suspicion of rebleeding was considered in patients who after an initial improvement developed one of the following : a decrease in systolic blood pressure (≤100 mmHg), tachycardia (≥100 beats per min), fall in hemoglobin (>20 g/L), no increase in hemoglobin levels with red blood cell transfusions, or re-occurrence of overt bleeding. Patients who had 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 intragastric fresh blood.

The threshold for blood transfusion was < 7 gm/dL in most cases. Extreme caution was taken during transfusion of these patients on hemodialysis to avoid volume overload. The patient who needed blood transfusion was given the least possible number of packed red blood cells during the session of heparin-free hemodialysis.

The primary outcome measure was the occurrence of rebleeding during the hospital stay, diagnosed at a repeat endoscopy. Secondary outcome measures included the need for surgical intervention, transfusion requirement, length of hospital stay, and mortality.

Statistical methods

IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA) was employed for statistical analysis. Numerical information was assigned as mean and standard deviation or median and range according to appropriateness. Frequency and percentage were used to express qualitative information. Chi-square test (Fisher's exact test) was employed to assess the relationship between qualitative variables. For quantitative information, the comparison between the two cohorts was performed employing independent sample t-test or Mann-Whitney test. A significant p-value was < 0.05.

Results

The two cohorts were compared in terms of the baseline features. There was a statistically significant difference between the two studied cohorts in age, and baseline

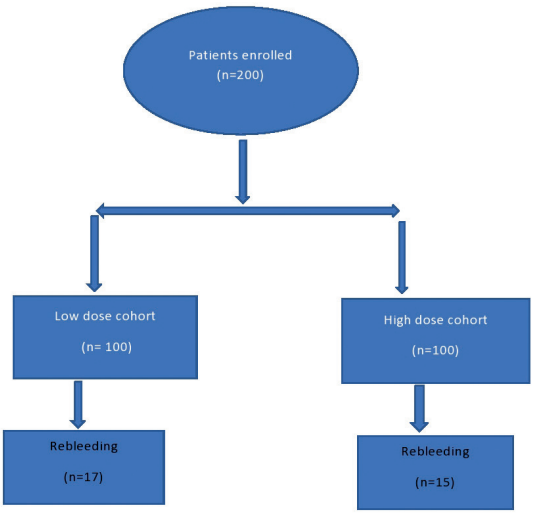

Figure 1. — Flow chart of patients included in the study.

Table 1. — **Characteristics of the two studied groups**

	High Dose n=100	**Low Dose n=100**	**p value**
Age (years)	53.3±8.3	55.7±7.7	0.034
Sex (Male/ Female)	60/40	59/41	0.885
Shock at presentation	35 (35.0%)	39 (39.0%)	0.558
Use of NASID or aspirin	50 (50.0%)	41 (41.0%)	0.201
Time from bleeding to endoscopy (hrs)			
<6	29 (29.0%)	24 (24.0%)	0.553
6-12	34 (34.0%)	29 (29.0%)	
12-24	22 (22.0%)	27 (27.0%)	
>24	15 (15.0%)	20 (20.0%)	
Previous ulcer disease	23 (23.0%)	35 (35.0%)	0.061
Previous history of bleeding	28 (28.0%)	22 (22.0%)	0.327
Serum creatinine (mg/dL)	6.0±0.9	5.7±1.2	0.020
Hemoglobin level (d/dL)	8.4±0.9	8.0±0.8	< 0.001
Site of the bleeding ulcer			
Gastric	37 (37.0%)	39 (39.0%)	0.771
Duodenal	63 (63.0%)	61 (61.0%)	
Ulcer size (mm)			
< 10	45 (45.0%)	36 (36.0%)	0.404
10-20	37 (37.0%)	41 (41.0%)	
> 20	18 (18.0%)	23 (23.0%)	
Forrest classification			
Ia- Spurting	15 (15.0%)	16 (16.0%)	0.745
Ib- Oozing	28 (28.0%)	34 (34.0%)	
IIa- Non-bleeding visible vessel	33 (33.0%)	27 (27.0%)	
IIb- Adherent clot	24 (24.0%)	23 (23.0%)	
Endoscopic hemostasis modality			
Unimodal	40 (40.0%)	43 (43.0%)	0.667
Bimodal	60 (60.0%)	57 (57.0%)	
Type of PPI used			
Esomeprazole	35 (35.0%)	37 (37.0%)	0.625
Omeprazole	35 (35.0%)	39 (39.0%)	
Pantoprazole	30 (30.0%)	24 (24.0%)	
Number of transfused packed RBCs	1 (0-4)	1 (0-4)	0.972
No. of patients need ≥ 2 units	29 (29%)	28 (28%)	0.876

Data are presented as mean±SD, median (range) or number (%).

serum creatinine and hemoglobin levels. However, the variability was within the clinically accepted ranges (Table 1).

Rebleeding occurred in 32 patients ; 15 in the High-Dose Cohort and 17 in the Low-Dose Cohort with no considerable difference between the two groups (p = 0.700) (Figure 1). The characteristics of patients with rebleeding in the two cohorts are shown in Table 2. There were no considerable differences between the two dose groups regarding the time of rebleeding (p = 0.243), endoscopic hemostasis mode (p = 1.000), and need for surgery (p = 0.306). Seventeen patients died with an in-hospital mortality rate of 8.5%. The high-dose regimen In-hospital mortality in high-dose group was 9.0% compared to 8.0% in the low-dose group (p = 0.800).

Apart from the pre-hemostatic Forrest classification of ulcers, there were no significant differences between patients with re-bleeding ulcers (n=32) and those with non-rebleeding (n=168) in their clinical characteristics (Table 3). Rebleeding was more common in class Ia, i.e. spurting bleeders (p < 0.001). Also, there was no considerable variation between the two cohorts in the period of hospitalization ; 8.1±1.6 days in the rebleeding group vs. 8.3±1.7 in those with no rebleeding (p = 0.211). Ulcer rebleeding was not significantly associated with higher in-hospital mortality ; 4 patients (12.5%) died in the rebleeding group compared to 13 (7.7%) in the non-rebleeding group (p = 0.376).

Discussion

The results of this work showed that high-dose PPIs do not offer more beneficial effect compared to low-dose PPIs in decreasing the rates of recurrent bleeding, surgical interference, or death post endoscopic hemostasis of bleeding peptic ulcers in cases on regular hemodialysis. Forrest classification of the bleeding ulcer was the only predictor of recurrent bleeding risk.

After initial resuscitation, endoscopic management remains the optimum treatment of high-risk ulcers. How-

Table 2. — **Characteristics of the 32 patients who developed rebleeding in the two studied groups**

	High Dose n=15	Low Dose n=17	p value
Time of rebleeding			
Within 3 days	9 (60.0%)	14 (82.4%)	0.243
After 3 days	6 (40.0%)	3 (17.6%)	
Forrest classification			
Ia- Spurting	8 (53.3%)	7 (41.2%)	*
Ib- Oozing	2 (13.3%)	3 (17.6%)	
IIa- Non-bleeding visible vessel	3 (20.0%)	4 (23.5%)	
IIb- Adherent clot	0 (0.0%)	0 (0.0%)	
IIc- Ulcers with a flat spot	1 (6.7%)	3 (17.6%)	
III- Clean base	1 (6.7%)	0 (0.0%)	
Endoscopic Hemostasis	13 (86.7%)	14 (82.4%)	1.000
Need for surgery	5 (33.3%)	3 (17.6%)	0.306

Data are presented as number (%). * no p-value due to the small number of cases in subgroups.

Table 3. — **Comparison between patients who developed rebleeding and those who didn't**

	Rebleeding n=32	No Rebleeding n=168	p value
Age (years)	54.8±9.4	54.4±7.8	0.837
Sex (Male/ Female)	21/11	98/70	0.441
Shock at presentation	15 (20.3%)	59 (79.7%)	0.207
Use of NASIDs or aspirin	10 (11.0%)	81 (89.0%)	0.077
Time from bleeding to endoscopy (hrs)			
<6	8 (15.1%)	45 (84.9%)	0.440
6-12	7 (11.1%)	56 (88.9%)	
12-24	11 (22.4%)	38 (77.6%)	
>24	6 (17.1%)	29 (82.9%)	
Previous ulcer disease	7 (12.1%)	51 (87.9%)	0.332
Previous bleeding history	7 (14.0%)	43 (86.0%)	0.656
Site of the bleeding ulcer			
Gastric	15 (19.7%)	61 (80.3%)	0.259
Duodenal	17 (13.7%)	107 (86.3%)	
Ulcer size (mm)			
< 10	8 (9.9%)	73 (90.1%)	0.073
10-20	18 (23.1%)	60 (76.9%)	
> 20	6 (14.6%)	35 (85.4%)	
Forrest classification			
Ia- Spurting	12 (38.7%)	19 (61.3%)	< 0.001
Ib- Oozing	10 (16.1%)	52 (83.9%)	
IIa- Non-bleeding visible vessel	9 (15.0%)	51 (85.0%)	
IIb- Adherent clot	1 (2.1%)	46 (97.9%)	
Endoscopic hemostasis modality			
Unimodal	9 (10.8%)	74 (89.2%)	0.094
Bimodal	23 (19.7%)	94 (80.3%)	
Type of PPI used			
Esomeprazole	9 (12.5%)	63 (87.5%)	0.251
Omeprazole	16 (21.6%)	58 (78.4%)	
Pantoprazole	7 (13.0%)	47 (87.0%)	
PPI Dose			
High Dose	15 (15.0%)	85 (85.0%)	0.700
Low Dose	17 (17.0%)	83 (83.0%)	

Data are presented as mean±SD or number (%).

ever, despite the advances in endoscopic techniques, rebleeding is still a threat to nearly 10% to 20% of patients with a mortality rate of 4% (19). Therefore, prevention of ulcer rebleeding is crucial to accomplish the mission of optimal management of emergency ulcer hemorrhage. Gastric acidity was shown to antagonize hemostasis inside the stomach and duodenum. It precludes clot synthesis and enhances lysis of existing clots. In vitro studies showed that platelet aggregation is compromised at gastric juice of pH 6.4. (20). In the current practice, acid suppression medication in combination with endoscopic therapy is the backbone of treatment of peptic ulcer

bleeding (21,22). A systematic review of 24 randomized controlled trials (RCTs) has demonstrated much superior efficacy of PPIs compared to H_2-receptor antagonists in this regard (19).

Yet, the best approach for post-endoscopy PPI dosing remains undefined. Consensus statements have recommended a high-dose PPI regimen (80 mg followed by an infusion of 8 mg/h for 72 h) to decrease recurrent bleeding and death in cases with high-risk stigmata (15,23,24). Other studies found low-dose regimens to be effective in reducing gastric acidity as well (25,26).

Many investigators initiated RCTs to compare the high dose-intensive approach with the standard regimen of 40 mg bolus daily ensued by saline infusion for 72 h. Andriulli et al. (27) did not find the high-dose regimen to be more effective in decreasing the rate of rebleeding after endoscopic hemostasis. Similar findings were reported by other investigators (28-31)

The main target of PPI administration is to keep gastric pH > 6 to promote clot stabilization in an ideal condition for cure of peptic ulcer (32). High-dose IV continuous PPI infusion is supposed to provide the most potent acid suppression. An intravenous bolus inhibits stimulated parietal cells with active proton pumps ; then continuous infusion can inactivate any newly synthesized proton pumps (33). Clinical studies did not support this theoretical advantage of the high-dose regimen. Javid et al. (34) compared the effect of IV infusion versus oral PPIs on intragastric pH following endoscopic therapy for a bleeding peptic ulcer. All patients attained a mean 72 h intragastric pH of >6 with no considerable variations between the oral and parenteral approaches.

The current study and many others (27-28,35) challenge the guidelines recommending an IV followed by continuous infusion PPI therapy (15,16,36,37). However, more recent guidelines suggest considering intermittent high doses of oral or intravenous PPI rather than continuous infusion (36,37). The current study supports intermittent standard doses of IV PPI.

On the other hand, the prevalence of cases with advanced chronic renal failure who requires hemodialysis constitutes a major load on the health budget. (38) Bleeding from the gastrointestinal tract is not uncommon is cases with end-stage renal disease. (39)

Past reports have demonstrated an increased risk of upper GI bleeding in these patients compared to the general population in addition to elevated death rates. (40)

To our knowledge, this is the first prospective work that compares high- versus low-dose PPI post-endoscopic hemostasis in this special group of patients on hemodialysis. Multiple factors make these patients a high-risk group of upper GI bleeding. These factors include uremia-related platelet dysfunction, old age, associated arteriovenous malformations, anemia, and numerous co-morbidities (11,12,41). These patients are commonly exposed to drugs that impacts the coagulation cascade such as non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelets, and anticoagulants (12,13). These factors contributes to higher risk of rebleeding, transfusions, longer hospital stay, surgical intervention, and mortality (42,43). The risk of rebleeding is enhanced up to one year after primary treatment (44).

In spite of this, the current work has some limitations. The principal limitation of this study was reporting only in-hospital outcome without post-discharge follow up. According to previous studies, rebleeding after discharge may occur, but bleeding mostly recurred within the first 72 h (28,45,46). It is probable we did not miss a high number of cases in view of the mean duration of hospital stay in the current study.

Another limitation is the non-randomized nature of the study that may affect the generalizability of the results. Further randomized studies are warranted for objective validation of the study outcomes.

Furthermore, it should be also noted that the recommendations of guidelines are against unimodal treatment because of high rebleeding risk. However, in this study, 40% of the patients had this type of hemostasis. This is largely related to limited resources which many centers are facing and this could have some potential influence on the results.

In summary, we can conclude the endoscopic hemostasis followed by the standard low-dose PPI strategy of 40 mg daily IV boluses are safe and effective treatment of bleeding peptic ulcers in the high-risk patients under regular hemodialysis. The high-dose continuous infusion regimen did not improve the treatment outcome in terms of rebleeding rate, need for surgery, hospital stay, and in-hospital mortality.

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