ORIGINAL PAPER

Role of Intravenous Omeprazole on Non-variceal Upper Gastrointestinal Bleeding After Endoscopic Treatment: a Comparative Study

Indrit Këlliçi[1], Bledar Kraja[2], Iris Mone[3], Skerdi Prifti[2]
Endoscopy Unit, University Hospital of Durres, Albania[1]
University Clinic of Gastrohepatology, University Hospital Center "Mother Theresa", Tirana, Albania[2]
Laboratory Department, University Hospital Center "Mother Theresa", Tirana, Albania[3]

Aim: To evaluate and compare the clinical efficacy of intravenous omeprazole versus intravenous ranitidine therapy for the treatment of non-variceal upper gastrointestinal (UGI) bleeding after endoscopic therapy. **Methods:** 108 patients (72 males and 36 females) admitted with non-variceal UGI bleeding in the Intensive Care Unit of the University Hospital of Durres, Albania, from 2004 to 2008, were included in the study. Patients with gastro-duodenal malignancy and those who were previously receiving anti-secretory drugs were excluded. All patients were treated endoscopically by injecting epinephrine (diluted 1:10.000) followed by ethanol and subsequently were randomized to receive either intravenous omeprazole (with an initial dose of 80 mg, followed by 8 mg/h infusion [n = 54]), or intravenous ranitidine (100 mg bolus, followed by 100 mg boluses every 6 hours for the next 72 hours [n = 54]). **Results:** The re-bleeding rate 72 hours after endoscopic treatment was lower in the omeprazole group than in the ranitidine group (6 vs. 14 patients, respectively; OR=3.4; 95% CI =1.1 –7.2; P<0.01). Less volume of blood transfusion was needed for the omeprazole group than for the ranitidine one (1.1 ± 1.8 units vs. 2.3 ± 2.9 units, P=0.03). The hospitalization period was shorter among patients treated with omeprazole than among those treated with ranitidine (5.4 ± 2.6 days vs. 6.8 ± 3.3 days, respectively; P=0.04). The need for surgery and the mortality rate were not statistically different between the two groups. **Conclusion:** After endoscopic treatment of non-variceal UGI bleeding, intravenous omeprazole reduced the risk of recurrent bleeding, decreased the need for blood transfusion and shortened the period of hospitalization. Intravenous omeprazole should be used in patients with non-variceal UGI bleeding after effective endoscopic treatment. ***Key words:*** bleeding, omeprazole, peptic ulcer, ranitidine.

Corresponding author: Bledar Kraja, MD. University Clinic of Gastrohepatology, University Hospital Center Mother Theresa, Tirana, Albania E-mail: bledarkraja@yahoo.com

1. INTRODUCTION

Non-variceal upper gastrointestinal (UGI) bleeding remains a major reason for hospitalization and mortality. Its overall incidence is approximately 150 hospital admissions per 100.000 inhabitants per year and the most common cause of UGI hemorrhage is peptic ulcer (1, 2). Most ulcers stop bleeding spontaneously as a result of intrinsic haemostatic mechanisms, but in one fifth of cases these mechanisms may fail, and the bleeding continues (2).

Endoscopic therapy for bleeding peptic ulcer is an important modality of treatment. A meta-analysis has shown that endoscopic treatment in such cases reduces the rates of recurrent bleeding, surgery and mortality (3). However bleeding recurs within 72 hours after endoscopic therapy in approximately 20% of patients and overall mortality of UGI bleeding remains around 10% (4,5).

Pharmacological treatment is an attractive adjuvant to endoscopy therapy in UGI bleeding. The major goal of the medical therapy is the inhibition of gastric acid secretion. The studies have shown that a high intragastric pH could facilitate platelet aggregation and removal of proteolitic influence of pepsin on thrombus (2,6,7). The intragastric pH above 6.0 for a minimum period of 72 hours is necessarily for clot stability at the ulcer site (8).

The intravenous use of Histamine H2-receptor antagonists (H2RA) or Proton Pump Inhibitors (PPI) inhibits the gastric secretion but the intravenous infusion of PPI maintains intra-

gastric pH above 6.0, showing better effect than H2RA administration (6,9). Thus, the intravenous use of PPI is theoretically superior in preventing recurrent bleeding.

Several studies have evaluated the effect of PPI on the non-variceal UGI bleeding (10,11,12,13). Unfortunately in some of them the results are not very clear because of including a heterogenic group of patients (10,11), or not performing any endoscopic treatment (12,13).

2. GOAL

The aim of our study was to evaluate the clinical effectivity of intravenous PPI therapy compared with intravenous H2RA for the treatment of non-variceal UGI bleeding after endoscopic therapy.

3. METHODS

Study population

Between June 2004 and August 2008, 173 patients with upper GI bleeding were admitted at the Intensive Care Unit of the University Hospital of Durres, Albania. All of them were diagnosed and eventually treated endoscopically. We included in our study the patients with non-variceal UGI bleeding older than 16 years in whom haemostatic endoscopy had been successful. We excluded patients with gastroduodenal malignancy and those previously treated with antisecretory drugs (H2RA or PPI).

Endoscopic therapy

Endoscopic examinations were performed using a video-endoscope (FUJINON 2200) within the first 24 hours of admission. Patients were treated endoscopically by injecting 10–25 cm^3 of adrenaline (epinephrine) (diluted 1:10 000) around the ulcer crater and absolute alcohol on the ulcer bed to stop the bleeding. Haemostasis was considered as established if bleeding had stopped and bleeding vessels were flattened or cavitated. In patients with non-bleeding visible vessels, haemostasis was considered as established when the vessel disappeared.

Data collection

After endoscopic treatment, patients were randomized to receive intravenous infusions of omeprazole or ranitidine for a period of 72 hours. They were divided into two groups according to the medical therapy: group I had received 80 mg intravenous omeprazole bolus, followed by an 8 mg/h infusion for 72 hours, and group II had received intravenous ranitidine 100 mg bolus, followed by 100 mg boluses every 6 hours for a period of 72 hours.

The following data were recorded on every patient: age, sex, location of the ulcer (stomach or duodenum), bleeding stigmata (visible vessel, oozing hemorrhage, spurting or clot), presence of shock, hemoglobin and hematocrit level, previous ulcer bleeding or ulcer disease, non-steroid anti-inflammatory drugs or aspirin use, and comorbid conditions. The Rockall scoring system was used to assess the severity of bleeding in both groups (14).

The primary end-point was 72-hours re-bleeding rate. Re-bleeding was defined as new hematemesis, melaena, or hypotension (< 100 mm Hg systolic blood pressure) associated with a drop in hemoglobin and/or endoscopic evidence of fresh re-bleeding. Volume of blood transfusion, hospital stay, need for surgery and mortality were considered as secondary end-points.

Statistical analysis

Data were entered into a personal computer and analyzed using the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as means (± standard deviations). The results of the two treatment groups were compared by chi square ($\chi 2$) test (categorical variables), and Student's t test (numerical variables). To test the association between outcomes and clinical co-variables, we estimated risk ratios and 95% confidence intervals (95%CI). In all analyses, statistical significance was considered at $P \leq 0.05$.

4. RESULTS

During the study period, a total of 173 patients with upper GI bleeding

Variable	Omeprazole Group (N=54)	Ranitidine Group (N=54)
Sex (no. of patients) Male Female	 35 19	 37 17
Age (in years)	55.4 4 17.3†	55.8 4 16.9
Hemoglobin (g/dl)	8.24 4 1.4	8.29 4 1.5
Hematocrit level (%)	27.7 4 4.2	27.5 4 3.7
Shock at presentation (no. of patients)‡	7	6
Location of ulcer (no. of patients) Stomach Duodenum	 15 39	 16 38
Endoscopic signs of bleeding (no. of patients) Visible vessel Oozing hemorrhage Spurting hemorrhage Clot with underlying vessel	 16 20 4 15	 12 19 3 19
Size of ulcer (in cm.)	1.06 4 0.8	1.12 4 1.0
Previous ulcer disease (no. of patients)	11	12
Previous ulcer bleeding (no. of patients)	5	4
Risk factors for bleeding ulcer (no. of patients) Use of NSAID Use of aspirin	 10 18	 11 26
Rockall score	5.2 4 1.8	5.1 4 1.7
Coexisting illnesses (no. of patients) Ischemic heart diseases Cerebral stroke Diabetes mellitus Hypertension Other diseases	 8 3 3 4 2	 10 2 2 5 4

Table 1. Base-line characteristics of the 108 patients. There was no statistically significant difference between the two groups. † Means 4 standard deviations. ‡ Shock was defined as a systolic blood pressure of 90 mm Hg or less, or a pulse rate of 110 beats per minute or more.

Variables	Omeprazole Group (N=54)	Ranitidine Group (N=54)	Relative Risk (95% CI)	P value
Recurrent bleeding (%)	6 (11.1)	14 (25.9)	3.4 (1.1-7.2)	<0.05
Volume of blood transfusion (units)	1.1 4 1.8*	2.3 4 2.9	___	<0.05
Hospital stay (days)	5.4 4 2.6*	6.8 4 3.3	___	<0.05
Surgery (%)	2	5	0.5 (0.09-2.8)	NS†
Death (%)	1	2	1.9 (1.5-2.3)	NS

Table 2. Clinical outcomes after endoscopic therapy and medical treatment * Means 4 standard deviations.† Not statistically significant (P>0.05).

were admitted to our Unit. We excluded from the study 28 patients with other gastro duodenal lesions who were not treated endoscopically or underwent surgery because of profuse bleeding, 23 patients with esophageal varices, 6 patients with gastric tumors, and 8 patients who had previously received antisecretory drugs, H2RA or PPI. Only 108 patients fulfilled the criteria to be included in our study. The mean age of the patients was 55.6 years (range: 17 – 85 years). We had 54 patients in group I (taking intravenous omeprazole) and 54 patients in group II (taking intravenous ranitidine).

There were no statistically significant differences between the two study groups on regard of age, the severity of bleeding at presentation, the location of ulcer, endoscopic signs of bleeding, risk factors for ulcers, and coexisting illnesses (Table 1).

Table 2 shows the clinical outcomes of this study. The re-bleeding rate after 72 hours of endoscopic treatment was lower in the omeprazole group than in the ranitidine group (6 vs. 14 patients, respectively; OR=3.4; 95% CI =1.1-7.2; P=0.003). The mean (±SD) number of units of blood transfused after endoscopy and medical treatment was significantly smaller in the omeprazole group than in the ranitidine group (1.1 ± 1.8 vs. 2.3 ± 2.9 units, P=0.03). The difference was probably related to treatment, since the mean number of units transfused before endoscopic treatment was similar in the two groups (0.9 ± 1.2 and 1.0 ± 1.4 units, respectively; P=0.45). The hospitalization period was shorter among patients treated with intravenous omeprazole than those treated with intravenous ranitidine (5.4 ± 2.6 days vs. 6.8 ± 3.3 days, respectively; P=0.04). Twenty patients (6 in the omeprazole group and 14 in the ranitidine group) who had recurrent bleeding underwent a second endoscopy. The endoscopic retreatment stopped the bleeding in 67% of the patients in omeprazole group (4/6), and in 64% of the patients in ranitidine group (9/14). The need for surgery was lower in the omeprazole group (two vs. five), but the difference was not significant (P=0.17). Also, the mortality rate was not statistically different between the two groups of the study. One patient (1.8%) died in the omeprazole group compared with 2 (3.7%) in ranitidine group (P=0.14). All the patients died because of coexisting illnesses.

5. DISCUSSION

The main findings of our study indicate that aggressive acid suppression with intravenous omeprazole significantly reduces the rate of recurrent bleeding, if compared with intravenous ranitidine in patients with non-variceal UGI bleeding after endoscopic schlerotherapy. Patients who were treated with intravenous omeprazole required fewer blood transfusions and had significantly shorter period of hospital stay. The need for surgery and the mortality rate were also lower in the omeprazole group, but these differences were not significant.

Several studies have evaluated the use of PPI in patients with non-variceal UGI bleeding. These studies have shown that patients who received intravenous PPI had significantly lower rate of recurrent bleeding than those who received H2RA or placebo (10,15,16). PPI also decreases the need for blood transfusions, the need for surgery, the mortality rate, and shortens the time of hospitalization (9,17).

In second reports, the use of intravenous omeprazole is shown ineffective in patients with upper gastrointestinal haemorrhage either with (18) or without endoscopic therapy (12). The study of Daneshmend et al. included patients with variceal bleeding, tumours, and peptic ulcers, but in these two studies, the authors used an 80 mg intravenous bolus of omeprazole followed by 40 mg every 8 hours. Two other studies found that intravenous omeprazole reduced the need for surgery if it was accompanied with endoscopic therapy, but they did not show if it reduced the rate of recurrent bleeding or mortality (19,20).

In our study, we enrolled patients with gastro-duodenal bleeding ulcers. All the patients were treated with endoscopic epinephrine and ethanol injection within the first 24 hours of admission. Adrenaline in doses of 20 ml solution 1: 10 000 leads to about 85-90% suppression of non-variceal UGI bleeding (21,22).

After endoscopic therapy we used 80 mg intravenous omeprazole bolus, followed by an 8 mg/h infusion for the next 72 hours. PPI are continuously being generated, and the half-life of omeprazole in the circulation is short (50 minutes), therefore it needs to be given more frequently (e.g. every 3 hours) or continuously (23). Recommended dose of PPI for prevention of non-variceal bleeding recurrences is 80 mg in bolus and subsequently through next 72 hours dosage of 8mg/hour (7,8). We used intravenous omeprazole because oral omeprazole may suppress acid production to a similar degree, but it may take several days before the pH is consistently above 6.0.

Omeprazole acts on K^+-H^+-ATPases pump situated in parietal cells and outside gastric sites, in renal and vascular smooth muscles (23,25). This can result in decreased renal function and vasoconstriction in blood vessels. In our patients the mortality rate was not significant between the two groups and the deaths were caused only by co-morbid conditions.

Our study had some limitations. We did not measure intra-gastric pH in our patients because the high dose of omeprazole, like the one we used, can maintain intra-gastric pH above 6.0 (6). Our patients were not examined for Helicobacter pylori presence. The prevalence of H. Pylori in Albanian popula-

tion is very high (26,27) and therefore we did not examine for this bacteria in this group of peptic ulcer patients.

6. CONCLUSION

We found that intravenous omeprazole reduce the risk of recurrent bleeding, decreased the need for blood transfusion and shortened the hospital stay in patients with non-variceal UGI bleeding after endoscopic epinephrine injection. It should be used in these patients after effective endoscopic treatment.

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