Oral versus intravenous omeprazole in management of bleeding peptic ulcer: a randomized, controlled trial

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Received: 1 December 2022
Revised: 7 December 2022
Accepted: 7 December 2022
Published: xx xx 2022

Al-Azhar Assiut Medical Journal 2022, ??:??–??

Background
Upper gastrointestinal bleeding (UGIB) is a common gastrointestinal emergency with significant morbidity and mortality. Intravenous (IV) route administration of proton pump inhibitors is more commonly used for prevention of bleeding; however, it is more expensive and invasive than the oral route. We, herein, compared between oral and IV omeprazole in patients with high-risk UGIB regarding outcome.
Patients and methods
Patients with high risk for rebleeding peptic ulcers were included. All patients initially received IV omeprazole, and then esophagogastroduodenoscopy with hemostatic procedure was done. Thereafter, the patients were allocated to group A, who received oral omeprazole, and group B, who received IV omeprazole. The patients were followed up for 2 weeks for signs of rebleeding. Reendoscopy, angioembolization, or surgery was provided when needed.
Results
The study included 189 patients (96 in group A and 93 in group B). Frequency of rebleeding was higher among patients in group B (40%) compared with those in group A (30%) (*P*: 0.1). Reendoscopy was more frequently required for patients in group B (16.1%) than those in group A (3.1%) (*P*<0.001). Surgery was mandatory for three (3.2%) patients in group B, whereas angioembolization was used nearly equally in both groups (31.3% in group A vs. 29% in group B). Admission to ICU was more frequently needed (*P*: 0.02) and the length of hospital stays was longer (*P*: 0.003) for patients of group B. Regarding UGIB-related deaths, three (3.1%) patients from each group died.
Conclusion
Oral omeprazole is not inferior to IV omeprazole as adjuvant therapy to control peptic ulcer bleeding and to reduce the frequency of rebleeding.

Keywords:
intravenous, omeprazole, oral, upper gastrointestinal bleeding

Al-Azhar Assiut Med J ??:??–??

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Introduction

Upper gastrointestinal bleeding (UGIB) is a common gastrointestinal emergency with significant morbidity and mortality [1]. Peptic ulcer disease (PUD) is the most common cause, accounting for ~50% of the episodes [2,3]. However, in Egypt, bleeding peptic ulcer comes second to bleeding varices in order of frequency (~30%) [4].

Gastric acid inhibits clot formation and promotes clot lyses and, therefore, disturbs hemostasis of ulcers in the stomach and duodenum. Consequently, reduction of gastric acid secretion could prevent ulcer rebleeding [5,6]. Intravenous (IV) proton pump inhibitors (PPIs) are effective as adjuvant pharmacotherapy in preventing rebleeding in patients with bleeding peptic ulcer [7]; they are one of the most potent drugs for acid reduction [8,9].

The optimal route, dose, and duration of PPI therapy after endoscopic therapy of a bleeding peptic ulcer remain controversial. Several studies have shown comparable efficacy of IV and oral PPI in treating ulcers with high risk of rebleeding after endoscopic therapy [10,11]. The higher cost of IV PPI compared with oral PPI represents a financial burden in developing countries.

In this study, we aimed to compare oral versus IV omeprazole among patients with peptic ulcers with high risk of rebleeding regarding outcome.

Patients and methods

Patients

A single-center, prospective, randomized, controlled trial was conducted in Assiut University Hospitals,

Al-Rajhi Liver and Gastroenterology Hospital, from December 2019 through November 2020.

Patients with UGIB attending the emergency department were recruited. We included patients with peptic ulcers of esophagus (lower part), stomach, and duodenum with one or more endoscopic signs of high risk for rebleeding according to the Forrest classification [12] [ulcer bed exhibiting active bleeding (spurting: Forrest la, and oozing: Forrest lb), nonbleeding visible vessel (Forrest lla), and adherent clot (Forrest llb)].

Exclusion criteria were pregnancy, age less than 18 years, ulcers with endoscopic signs suspicious for malignancy, other sources of UGIB, low platelet count (less than 50 000 cc), prothrombin time more than 14 s, prothrombin concentration less than 30%, using anticoagulants, renal failure, and PPI use 14 days or less before admission.

Methods

Clinical evaluation was done for all included patients, including measurements for orthostatic hypotension and vital signs every 4 h during the first 24 h, then every 8 h during the remaining period of hospital stay. In addition, abdominal ultrasonography and laboratory investigations were provided for all the patients, including complete blood count (with daily estimation of hemoglobin level and hematocrit value), serum creatinine and blood urea levels, and prothrombin time and concentration. Before the initial esophagogastroduodenoscopy (EGD), all the patients were given IV omeprazole (80 mg, by IV infusion over 30 min).

Initial endoscopic evaluation (after resuscitation) for all the patients, by diagnostic EGD using Pentax EG-29I10 Video Gastroscope, included Forrest classification to assess risk for rebleeding. Only patients with high-risk signs of rebleeding were included. After endoscopy (with initial hemostasis), the patients were randomly allocated into two groups: group A patients received oral omeprazole (40 mg/12 h, for 72 h), whereas group B patients received IV omeprazole (8 mg/h, continuous infusion for 72 h). Randomization was done using the random selection function of SPSS software (version 22, Chicago, Illinois, USA). After the first 72 h, patients of both groups received oral omeprazole (40 mg/12 h). After the initial endoscopy, the Rockall score [13] was calculated to predict mortality and risk for rebleeding.

Rebleeding was suspected (during 24-h period) with one or more of the following criteria: recurrence of hematemesis and/or melena, orthostatic hypotension, abnormal vital signs (systolic blood pressure <90 mmHg and pulse rate >120 min), or reduction of hemoglobin level >2 g/dl (despite blood transfusion). For all patients with suspected rebleeding, urgent 'second-look' EGD was carried out.

From all patients, biopsies were taken from the antrum for histopathological examination. Patients that were positive for *Helicobacter pylori* were treated with standard-of-care triple therapy (omeprazole, 20 mg, amoxicillin 1000 mg, clarithromycin 500 mg; all twice daily, orally) for 2 weeks, after control of bleeding.

After discharge, follow-up included phone contact with weekly clinic visits for history taking (melena or hematemesis), blood pressure measurement, and hemoglobin level assessment.

The primary outcome of the study was recurrent UGIB within 15 days, whereas the second outcomes were length of hospital stay, admission to ICU, blood transfusion, need for angioembolization and/or surgery for uncontrolled recurrent bleeding, and mortality within 2 weeks.

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics, version 25.0, release 25.0.0.0; IBM Corp., Armonk, New York, USA) for Microsoft Windows. Results were expressed as mean SD or frequency (percentage) as appropriate. We compared outcome among the two groups of the study population using univariate analyses (Student's t test or Mann–Whitney U test for continuous data, and Yates' corrected χ^2 test or Fischer's exact test for categorical data).

The software G*Power, version 3.1.9.2 was used for a post-hoc power analysis of the performed χ^2 tests. An arbitrary effect size was chosen for the power analysis, which precisely was a Cohen's w statistic of 0.4. This value conventionally corresponds to a medium-sized effect. A power of 85% was achieved to detect a medium-sized effect.

Ethical considerations

The study was approved by the Clinical Research Ethical Committee of Assiut Faculty of Medicine (IRB 00008717) and carried out according to the code of ethics of the World Medical Association

(Declaration of Helsinki). The study was registered in Clinicaltrials.gov (NCT04170270). All the participants signed a written informed consent.

Results

A total of 1000 patients with UGIB were evaluated during the study period. After exclusion of 800 patients, only 200 were eligible. They were randomly allocated into two groups: 100 in group A (oral group) and another 100 in group B (IV group). During follow-up of the study patients, four patients of group A and seven of group B did not comply with the follow-up and were excluded.

Table 1 Baseline demographic and clinical data of the study population

	Group A (*N*=96)	Group B (*N*=93)	*P* value
Age (years)	52.66±18.37	58.52±14.24	0.01
Male sex	66 (68.8)	84 (90.3)	<0.001*
Smoking	30 (31.3)	33 (35.5)	0.32
Clopidogrel use	9 (9.4)	12 (12.9)	0.29
Aspirin use	48 (50)	36 (38.7)	0.07
History of PUD	6 (6.3)	24 (25.8)	<0.001*
DM	16 (16.7)	19 (20.4)	0.31
HTN	22 (22.9)	11 (11.8)	0.03*
IHD	3 (3.1)	16 (17.2)	<0.001*
CKD	3 (3.1)	6 (6.5)	0.23
Liver disease	9 (9.4)	3 (3.2)	0.07
Other comorbidities	3 (3.1)	3 (3.2)	0.64

Data were expressed as frequency (percentage) or mean (SD). CKD, chronic kidney disease; DM, diabetes mellitus; HTN, systemic hypertension; IHD, ischemic heart disease; PUD, peptic ulcer disease. Group A, received oral omeprazole; group B, received intravenous omeprazole. *Statistically significant.

Basic clinical, laboratory, and imaging characteristics

Table 1 shows the characteristics of the study population. The mean age was significantly lower among patients in group A, with predominance of male sex when compared with those in group B. Systemic hypertension (*P*: 0.03), ischemic heart disease (*P*<0.001), and history of PUD (*P*<0.001) were significantly more frequent among patients in group B compared with those in group A.

Table 2 shows severity parameters of acute UGIB among the study population. All the parameters were higher among patients in group B when compared with those in group A.

Table 2 Risk stratification of the study population

	Group A (*N*=96)	Group B (*N*=93)	*P* value
Shock	3 (3.2)	15 (16.1)	0.003*
Hemoglobin (g/dl)	8.11±2.20	5.76±2.36	<0.001*
Rockall score	3.68±1.11	4.74±1.77	<0.001*
Blood transfusion	84 (87.5)	90 (96.8)	0.01*

Data were expressed as frequency (percentage) or mean (SD). Group A, received oral omeprazole; group B, received intravenous omeprazole. *Statistically significant.

Table 3 Endoscopic findings of the study population

	Group A (*N*=96)	Group B (*N*=93)	*P* value
Site of ulcer			<0.001*
Esophagus	0	3 (3.2)	
Gastric body	24 (25)	18 (19.4)	
Antrum	6 (6.3)	0	
Prepyloric area	3 (3.1)	0	
Duodenum	45 (46.9)	48 (51.6)	
Multiple sites	18 (18.75)	24 (25.8)	
Number of ulcers			0.17
Single	60 (62.5)	51 (54.8)	
Multiple	36 (37.5)	42 (45.2)	
Size of ulcer			<0.001*
Large (>20 mm)	46 (47.9)	30 (32.3)	
Small	50 (52.1)	63 (67.7)	
Forrest class			<0.001*
Class Ia	23 (34.4)	21 (22.6)	
Class Ib	12 (12.5)	3 (3.2)	
Class IIa	12 (12.5)	9 (9.7)	
Class IIb	39 (40.6)	60 (64.5)	
Positive *Helicobacter pylori*	36 (41.4)	36 (40)	0.48
Clipping	27 (28.1)	12 (12.9)	0.03*
Adrenaline injection	9 (9.4)	9 (9.6)	

Data were expressed as frequency (percentage). Group A, received oral omeprazole; group B, received intravenous omeprazole. *Statistically significant.

Regarding the endoscopic findings among our study population, as shown in Table 3, the most frequent site of ulcers was duodenum. Small, solitary ulcer was the most frequent endoscopic finding in both groups. Multiple ulcers were more frequent among patients in group B (45.2%) compared with those in group A (37.5%), with no statistically significant difference. Large ulcers were significantly more frequent among patients in group A (47.9%) compared with those in group B (32.2%) ($P<0.001$). Regarding Forrest classification, Forrest IIb ulcer (adherent blood clot) was the most frequently reported class among patients in both groups. It was significantly more frequent among patients in group B (64.5%) compared with those in group A (40.6%) ($P<0.001$).

Clipping was more frequently needed for patients in group A (28.1%) compared with only 12.9% of those in group B during the first endoscopy ($P=0.03$), whereas adrenaline injection was equally performed among patients of both groups (9.4%).

Table 4 shows therapeutic outcomes among the study population. Rebleeding was more frequent in patients in group B (40%) compared with those in group A (30%), with no statistically significant difference (P: 0.1). However, reendoscopy was significantly more frequently required for patients in group B (16.1%) when compared with those in group A (3.1%) ($P<0.001$). Surgery was needed in only three (3.2%) patients of group B, whereas angioembolization was needed nearly equally in both groups (31.3% in group A and 29% in group B). Admission to ICU was significantly more frequently needed (P: 0.02) and length of hospital stays were significantly longer (P: 0.003) for patients of group B compared with those of group A. Regarding UGIB-related deaths, mortality rate was 3.1% among patients of both groups. Non-UGIB-related deaths were only among six patients of group A (myocardial infarction in three patients and pneumonia in three patients).

Discussion

PPIs are effective adjuvant therapy for patients with UGIB. By inhibiting acid secretion, they prevent clot lysis and so enhance hemostasis of bleeding ulcers. Oral route of administration has lower cost and more availability when compared with IV route; however, debate exists regarding which is more efficacious. In our study, we aimed to compare oral with IV administration of omeprazole for patients with bleeding ulcers who have high rebleeding risk.

Endoscopic examination of our patients revealed that the most frequent site of PUD was the duodenum. This is comparable to the results of Yen *et al.* [14], where duodenal ulcers were more common in patients with UGIB. However, Mostaghni *et al.* [15] reported more prevalent gastric ulcers. In our study, solitary and small ulcers (<20 mm) were more common than multiple and large ulcers, in agreement with Sung *et al.* [11] and Javid *et al.* [16]. Regarding Forrest classification, class IIb was the most prevalent. Contradictory to our results, Sung *et al.* [11] found that class IIa was the most frequent. In our study, clipping was more frequently used than adrenaline injection for control of rebleeding, whereas Sung *et al.* [11] used the application of heater probe more frequently followed by clipping. In our study, we followed recommendations stating that application of clipping is superior to injection alone for definitive hemostasis, and use of epinephrine injection alone should be avoided [17].

When comparing both groups of our study population, it was found that severity of UGIB (as manifested by shock, anemia, and requirement of blood transfusion)

Table 4 Therapeutic outcomes of the study population

	Group A (N=96)	Group B (N=93)	P value
Rebleeding	27 (30)	36 (40)	0.10
Reendoscopy	3 (3.1)	15 (16.1)	<0.001*
Surgical intervention	0	3 (3.2)	0.11
Angioembolization	30 (31.3)	27 (29)	0.43
ICU admission	57 (59.4)	69 (74.2)	0.02*
Hospital stays (days)	6.34±1.89	7.94±4.81	0.003*
Outcome			0.04*
Alive	93 (96.9)	84 (90.3)	
Died secondary to bleeding	3 (3.1)	3 (3.2)	
Died secondary to other cause	0	6 (6.5)	

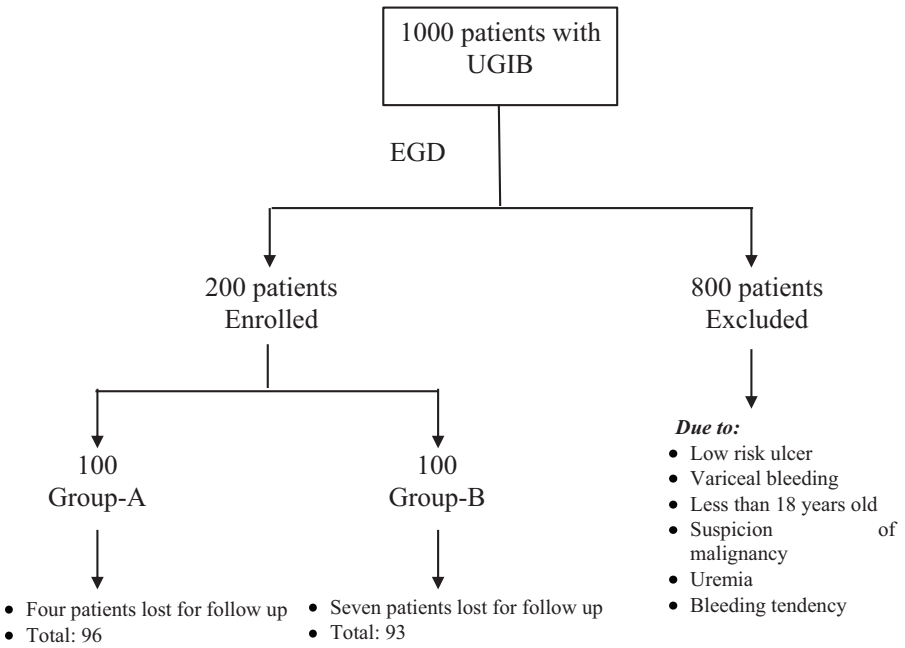
Data were expressed as frequency (percentage). Group A, received oral omeprazole; group B, received intravenous omeprazole.
*Statistically significant.

and risk of rebleeding (Rockall score) were higher among group B patients. Similar results were reported by previous studies of Mostaghni *et al.* [15] and Karim *et al.* [18]. They found that significantly higher mean volume of packed cells was need for transfusion among patients who received IV PPI. In addition, Sung *et al.* [11] found that systolic blood pressure, hemoglobin level, and blood transfusion requirement were similar for patients receiving IV or oral PPI. Two meta-analyses by Csiki *et al.* [19] and by Tringali *et al.* [20] showed no statistically significance difference for any of the outcomes considered in subgroup analysis when comparing high-dose oral PPI with high-dose IV PPI, except for blood transfusion, which was more frequent among patients who received oral PPI. In our study, blood transfusion was more frequently indicated for group B patients.

Regarding the therapeutic outcome among our study population, rebleeding was more frequent among patients of group B (40%) compared with those of group A (30%), and consequently, reendoscopy was required more frequently for the patients of group B (16.1%) when compared with those of group A (3.1%). Sung *et al.* [11] reported comparable frequency of rebleeding between patients who received oral PPI and those who received IV PPI; moreover, the frequency of reendoscopy was similar in both groups, which was agreed upon by findings of a meta-analysis conducted by Csiki *et al.* [19] including ~2000 patients from 14 RCTs. A higher incidence of rebleeding in group B patients in our study can be explained by more frequent comorbidities among such patients (older age, history of PUD, and ischemic heart disease) when compared with those of group A. Regarding angioembolization, it was approximately equally required for the patients of both groups; however, surgical intervention was mandatory for a small percentage of group B patients. In the study by Nykänen *et al.* [21], transarterial embolization or surgery was necessary for 5.4% of the patients. Similarly, Jairath *et al.* [22] reported that 3.6% of patients with nonvariceal UGIB required salvage therapy with surgery or arterial embolization. This frequency is far less than what we found, where angioembolization was only necessary for 30% of our study population. Including patients with high risk for rebleeding may explain the higher frequency of angioembolization for our study patients.

Regarding hospital stay, we found that it was longer in group B patients who received IV omeprazole. Tsai *et al.* [23] concluded that hospital stay is equal in patients who received oral rabeprazole and patients who received IV omeprazole. Yen *et al.* [24] also concluded the same results when comparing oral lansoprazole with IV esomeprazole.

Figure 1



Study flow chart. EGD, esophagogastroduodenoscopy; group A, received oral omeprazole; group B, received intravenous omeprazole; UGIB, upper gastrointestinal bleeding.

Conclusion

The outcomes of our patients treated with oral omeprazole were better than those of patients who received IV omeprazole. However, this conclusion must be considered in light of higher frequency of some risk factors for rebleeding among the patients of IV group. In real life, we expect to get an equal outcome for the two groups. Overall, we can conclude that oral omeprazole is not inferior to IV omeprazole in patients with high risk UGIB. Oral therapy is more cost effective (less price and shorter hospital stays) when compared with IV therapy. In addition, oral PPI administration is easy and needs no monitoring for the infusion site reactions such as edema and thrombophlebitis.

Limitations of our study included absence of blinding and lack of randomization regarding the different endoscopic tools used for hemostasis. Further studies with larger sample size, blinding, randomization of endoscopic tools for hemostasis, and using different agents of PPI group are recommended (Fig. 1).

Acknowledgements

Availability of data and materials: all datasets on which the conclusions of the manuscript rely are presented in the main paper.

Conflicts of interest

There are no conflicts of interest.

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