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RAPID COMMUNICATION

A head to head comparison of oral *vs* intravenous omeprazole for patients with bleeding peptic ulcers with a clean base, flat spots and adherent clots

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Abstract

AIM: To compare the effect of intravenous and oral omeprazole in patients with bleeding peptic ulcers without high-risk stigmata.

METHODS: This randomized study included 211 patients [112 receiving *iv* omeprazole protocol (Group 1), 99 receiving *po* omeprazole 40 mg every 12 h (Group 2)] with a mean age of 52.7. In 144 patients the ulcers showed a clean base, and in 46 the ulcers showed flat spots and in 21 old adherent clots. The endpoints were re-bleeding, surgery, hospital stay, blood transfusion and death. After discharge, re-bleeding and death were re-evaluated within 30 d.

RESULTS: The study groups were similar with respect to baseline characteristics. Re-bleeding was recorded in 5 patients of Group 1 and in 4 patients of Group 2 (P = 0.879). Three patients in Group 1 and 2 in Group 2 underwent surgery (P = 0.773). The mean length of hospital stay was 4.6 ± 1.6 d in Group 1 *vs* 4.5 ± 2.6 d in Group 2 (P = 0.710); the mean amounts of blood transfusion were 1.9 ± 1.1 units in Group 1 *vs* 2.1 ± 1.7 units in Group 2 (P = 0.350). Four patients, two in each group died (P = 0.981). After discharge, a new bleeding occurred in 2 patients of Group 1 and in 1 patient of Group 2, and one patient from Group 1 died.

CONCLUSION: We demonstrate that the effect of oral omeprazole is as effective as intravenous therapy in terms of re-bleeding, surgery, transfusion requirements, hospitalization and mortality in patients with bleeding ulcers with low risk stigmata. These patients can be treated effectively with oral omeprazole.

Key words: Oral omeprazole; Peptic ulcer; Bleeding

INTRODUCTION

Acute upper gastrointestinal (UGI) bleeding remains the most common reason for emergency hospital admission managed by gastroenterologists. It is reported that it has an annual incidence ranging from approximately 50 to 150 per 100 000 of the population[1], and it is still rising steadily in the aspirin/nonsteroidal antiinflammatory drugs (NSAIDs) era. The most common cause of UGI bleeding in adult patients is peptic ulcer disease, which accounts for about 50% of the cases[2]. Patients with peptic ulcer bleeding account for an overall mortality rate that has remained around 5%-10% for the past five decades, despite improved therapy options and the availability of intensive care units[3].

Previous consensus guidelines and several studies have demonstrated that the risk for re-bleeding or continued bleeding from an ulcer is strongly associated with the stigmata seen at endoscopic examinations[4-7]. These hemorrhagic stigmata consist of a clean ulcer base, flat spots, adherent clots, nonbleeding visible vessels and active bleeding (oozing and spurting). Major stigmata of recent hemorrhage include spurting, oozing vessels, nonbleeding visible vessels or fresh adherent clots, while an old adherent clot was considered as minor stigmata[8]. There are also several studies that classified the high-risk stigmata as spurting, oozing, or nonbleeding visible vessels, excluding all adherent clots[9,10]. Currently, endoscopic hemostatic therapy is strongly recommended in patients with arterial spurting, oozing ulcers and nonbleeding visible vessels[11,12]. The optimum management of adherent clots has long been controversial. Although there are studies with opposite conclusions in this field[13,14], a cited meta-analysis showed that endoscopic therapy is of significant benefit in patients with active bleeding or a visible vessel but not in patients with adherent clots[15].

The overuse of parenteral proton pump inhibitors (PPI) in UGI bleeding is a common practice all over the world.

A recent meta-analysis pointed out that both intravenous (*iv*) and oral (*po*) PPIs are effective in UGI bleeding. However, the mortality is increased with *iv* PPI in the same report[16]. Moreover, it is reported that most patients who present with ulcer bleeding have low-risk stigmata and do not require *iv* PPI treatment but can be appropriately and adequately treated with oral PPIs in clinical practice[17]. In case intravenous treatment is particularly expensive, oral treatment would be appropriate.

Most previous studies on omeprazole have been performed with *iv* administration and not with *po* form. It is known that most physicians do not prefer *iv* PPI in patients with low-risk ulcers. In spite of this view, the issue needs a better confirmation. In the literature there are an abundant number of studies that compare oral PPI *vs* placebo, with[18] or without[19] endoscopic therapy, *iv* PPI *vs* placebo[20] or oral PPI *vs* endoscopic injection[11]. At the same time, to the best of our knowledge, there is no study in the literature that has been designed to allow head-to-head comparison of oral *vs* intravenous PPI treatment in UGI bleeding. We therefore designed this study to make a comparison of oral and intravenous omeprazole in patients with bleeding peptic ulcers without high-risk stigmata, in terms of re-bleeding, surgery, hospital stay, blood transfusion and mortality. We believe that it is important to add stronger study-supported evidence to the literature in this population.

MATERIALS AND METHODS

Patients, definitions and study design

Patients were enrolled in the study if they had any symptoms of upper gastrointestinal bleeding, such as hematemesis, melena or the presence of blood in a patient' s nasogastric tube lavage. They were all older than 18 years. Informed consent to participate in the study was obtained from all patients and the study was performed in accordance with the principles stated in the Declaration of Helsinki. Exclusion criteria were as follows: (1) a history of chronic liver disease and portal hypertension, (2) gastroduodenal malignancy, (3) gastric surgery, (4) known adverse drug reactions to the trial drugs, (5) current use of antisecretory drugs, H_2-receptor antagonists or PPIs, (6) a history of endoscopic therapy for bleeding ulcer within the past four weeks, (7) pregnancy or lactation, (8) had endoscopic findings of active bleeding (spurting, oozing vessels or nonbleeding visible vessels), (9) refusal to provide written informed consent. Moreover, patients found to have malignant ulcers after initial enrolment were also excluded.

Gender, age, current smoking, alcohol consumption, comorbid medical illnesses, use of aspirin/NSAIDs (any dose within last week), prior epigastric pain, history of previous upper gastrointestinal bleeding, prior major surgery, concomitant use of anticoagulants, antithrombocytic agents other than aspirin, and steroids and previous eradication treatment for *H pylori,* were investigated. The spectra of the comorbid illnesses included chronic obstructive pulmonary disease, pneumonia, end-stage renal disease with hemodialysis, chronic renal insufficiency or acute renal failure, congestive heart failure, coronary artery disease and cerebrovascular accident. Besides, we recorded the duration of hospitalization, number of re-bleeding episodes, initial hemoglobin level, coagulation parameters, need for blood transfusion, the endoscopic data and addresses/phone numbers of all patients.

Endoscopic examinations were performed using a videoendoscope (Olympus GIF-V70, Tokyo, Japan) within the first 24 h of admission. At endoscopy all primary and secondary lesions were recorded. The coagulation factors (prothrombin time, partial thromboplastin time, platelet count) were checked and corrected prior to any endoscopic intervention, if needed. Patients with an underlying anatomic cardiac abnormality were considered at a high risk for endocarditis, and recommended antibiotic regimens were given. An ulcer was defined as a circumscribed mucosal break at least 5 mm in diameter and with a perceptible depth. The ulcer size was measured using biopsy forceps, of which the fully opened cup was 5 mm in diameter. Besides, stigmata of recent hemorrhage were recorded. A 'fresh' adherent clot was defined as the presence of an adherent clot over the ulcer that could not be dislodged by vigorous washing with a jet of water delivered through the channel of the endoscope[21]. An 'old' clot was defined, on the contrary, as a clot dislodged easily by washing. These lesions were also excluded from the study due to their needs for an endoscopic therapy. All patients with benign gastroduodenal ulcers showing a clean ulcer base, flat spots or old adherent clots at endoscopy were included in the study. During the emergency admission, oral anticoagulant therapy was stopped in users and coagulation was corrected when applicable. The criteria for blood transfusion were as follows: hemoglobin levels of lower than 9 g/dL in older than 65 years, hemoglobin levels of lower than 8 g/dL in younger patients, or if the patient had a new episode of hematemesis in both age groups. Besides, if a state of shock existed, blood was transfused independent of haemoglobin levels. All patients with upper gastrointestinal bleeding were examined for *H pylori* in biopsy specimens taken from the antrum by hematoxylin and eosin (HE) staining.

We performed a single-center randomized clinical trial, comparing the effect of high dose intravenous omeprazole (Group 1) and oral omeprazole (Group 2) on bleeding peptic ulcer. The study was conducted between January 2004 and August 2006 at Gastroenterology Clinic of Dicle University Research Hospital in Turkey. After a stabilization period, patients were randomly divided into two groups in the endoscopy laboratory. A person outside from the study staff placed the two drug formulations into sealed non-transparent envelops and coded them based on random table numbers. Only this person knew the codes. The research assistant, other medical personnel, the endoscopists, and patients were blind to this information. The study was conducted in a double-blind manner as all treatment assignments were revealed at the end of the study. The high dose intravenous group received a bolus injection of omeprazole (Losec®, AstraZeneca, Molndal, Sweden), 80 mg, given at admission, followed immediately by a continuous infusion of 8 mg/h for 72 h, then 40

mg orally daily for 6 wk. The other group received oral omeprazole (Omeprol®, Ilsan-Hexal (Sandoz), Gebze, Turkey) 80 mg a day (20 mg capsule, two in the morning and two in the evening) for 72 h, then 40 mg orally daily for 6 wk. It is well-known that PPI treatment is an essential option in bleeding peptic ulcers and we did not include a placebo group for each treatment due to ethical problems.

The primary endpoints of the study were recurrent bleeding (early re-bleeding), surgery requirement, and death rates before discharge. Re-bleeding was defined as new hematemesis, melaena, or hypotension (< 100 mm Hg systolic blood pressure) associated with a drop in haemoglobin and/or endoscopic evidence of fresh re-bleeding. Patients with recurrent bleeding underwent urgent second endoscopy for confirmation and the lesion was classified as in previous description. Surgical intervention was considered if the bleeding could not be controlled by endoscopic therapy. Shock was defined as a pulse rate > 100 beats/min, systolic blood pressure < 100 mmHg accompanied by cold sweats, pallor, and oliguria. Secondary endpoints were duration of hospital stay, blood transfusion requirement, and re-bleeding or death within 1 mo after index bleeding (late re-bleeding). All patients were also evaluated in terms of risk analysis by Rockall scoring system, which is based on five variables (age, presence of shock, comorbidity, endoscopic diagnosis, and endoscopic stigmata)[22].

Follow-up

Each patient was visited in the ward daily by a clinical research assistant who recorded information about their condition, their management, and results. After the treatment procedures, we observed the patients for complications such as recurrent bleeding, perforation or death in the hospital. Blood pressure and pulse rate were monitored hourly during the first 24 h and every 4 h, hemoglobin levels every 4 h during the first day and daily thereafter until discharge. Those who had no evidence of recurrent bleeding were discharged as soon as possible. After a treatment protocol of 72 h, patients with histologically proven *H pylori* were prescribed a 2-wk course of full dose omeprazole, twice daily, amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily, irrespective of the treatment protocol. In addition, we recommended them not to use aspirin/NSAIDs if not needed anymore or use them in combination with PPIs. After discharge, all of the patients were informed about our contact phone number and the patients or their relatives were asked to report to us if any re-bleeding or death occurred within 30 d.

Statistical analysis

Data were entered into a personal computer and analysed using the Epi-INFO 2000 software package (version 2000, CDC, Atlanta). Continuous variables were presented as mean (standard deviation). The results of the two treatment groups were compared by χ^2 test, Student's *t* test and Fisher's exact tests in the analysis as appropriate. To test the association between outcomes and clinical covariables, we estimated risk ratios and 95% CI. In all analyses, statistical significance was defined as $P < 0.05$.

RESULTS

During the study period, a total of 278 patients with bleeding gastroduodenal ulcers were admitted to our clinic. Of these ulcers, 21 were actively bleeding, 17 had nonbleeding visible vessels and 17 had a fresh adherent clot. At the beginning, all these 55 patients, together with 5 patients with malignant ulcer presentation, 4 patients currently known to take antisecretory drugs, H_2-RAs or PPIs and 3 patients with gastric surgery were excluded from the study.

Thus, a total of 211 eligible patients were included in the study and all of them completed the treatment protocols. The mean age of the patients was 52.7 (range, 18-93 years). The total number of patients with duodenal ulcer was 160 (75.8%) and gastric ulcer 51 (24.2%). Of the ulcers, 144 (68.2%) had a clean base, 46 (21.8%) had flat spots and 21 (10.0%) had old adherent clots. There were 112 patients in Group 1 (taking *iv* omeprazole) and 99 patients in Group2 (taking *po* omeprazole). The study groups were similar with respect to gender, age, stigmata of ulcer hemorrhage, use of aspirin/NSAIDs, *H pylori* status and previous eradication treatment, co-existing illnesses, previous abdominal surgery, alcohol consumption, smoking habit, previous epigastric pain, previous UGI bleeding, hematemesis, coagulopathy, shock, hematocrit, ulcer site (gastric-duodenal) and size. The characteristics of patients in both groups are summarized in Table 1. Multiple ulcers were found to be more common in Group 2 compared to Group 1 (6 and 17, respectively, $P = 0.007$). Besides, gastric antral and corporal ulcers were more common in Group 2 compared to Group 1 (33 *vs* 18, respectively, $P = 0.007$), while the number of duodenal anterior and posterior ulcers was similar in both groups. *H pylori* infection was present in 61.2% patients with duodenal ulcer and 41.2% patients with gastric ulcer ($P = 0.012$). Aspirin/NSAID use was recorded in 82% of gastric ulcers, while in 62% of duodenal ulcers ($P = 0.007$).

Clinical outcomes during hospital stay (inpatient basis)

Recovery without major complications was seen in 107 (95.5%) patients of Group 1 and in 95 (96.0%) patients of Group 2 ($P = 0.945$). Recurrent bleeding was recorded in 5 (4.5%) patients assigned to Group 1 and 4 (4.0%) patients assigned to Group 2 ($P = 0.879$, Fisher's exact test). Re-bleeding rates were similar between duodenal and gastric ulcers, and posterior duodenal and gastric corporal ulcers ($P = 0.511$ and 0.673, respectively. Fisher's exact test). Only one ulcer with a clean base (11.1%), while 3 ulcers with old clots (33.3%) and 5 with flat spots (55.5%) showed rebleeding.

Three patients (2.7%) in Group 1 and 2 (2.0%) in Group 2 underwent surgery to control re-bleeding after a failure in second endoscopic intervention ($P = 0.773$, Fisher's exact test). Surgery requirement was mostly seen in patients taking aspirin/NSAIDs in both groups (2, for each). Four patients (1.9%), two in each group died ($P = 0.981$, Fisher's exact test). Three were older than 65 years. The Rockall score higher than 8 was present in 18.1% of Group 1 and 19.1% of Group 2. The causes of death were pneumonia in 2, myocardial infarction in 1 and pneumonia

Table 1 Baseline characteristics of the study groups

Characteristics	Group 1 (*iv*) (*n* = 112)	Group 2 (*po*) (*n* = 99)	Total (*n* = 211)	*P*
Male / Female (*n*)	79/33	66/33	145/66	0.545
Age (mean ± SD)	52.7 ± 17.05	52.8 ± 19.61	52.7 ± 18.12	0.966[1]
Age < 65 yr [*n* (%)]	80 (71.4)	64 (64.6)	144 (68.2)	0.291
Age ⩾ 65 yr [*n* (%)]	32 (28.6)	35 (35.4)	67 (31.8)	
Ulcer site (*n*):				
-Duodenal	94	76	160	0.083
-Gastric	18	23	51	
Endoscopic signs (*n*):				
-Clean base	82	62	144	0.244
-Flat spot	20	26	46	
-Old adherent clot	10	11	21	
Ulcer size (cm)	1.05 ± 0.4	1.06 ± 0.6	1.05 ± 0.5	0.934[1]
Ulcer count (*n*):				
-Single	106	82	188	0.007[2]
-Multiple	6	17	23	
Ulcer locations (*n*):				
-Posterior duodenal	61	52	113	
-Anterior duodenal	33	14	47	0.007
-Gastric corporal	9	16	25	
-Gastric antral	9	17	26	
Aspirin/NSAIDs use [*n* (%)]	68 (60.7)	70 (70.7)	138 (65.4)	0.072
H pylori positive [*n* (%)]	63 (56.3)	56 (56.6)	119 (56.4)	0.963
Previous eradication [*n* (%)]	10 (8.9)	3 (3.0)	13 (6.2)	0.09[2]
Coexisting illness [*n* (%)]	41 (36.6)	35 (35.4)	76 (36.1)	
-Cardiac (*n*)	18	14	32	0.850
-Pulmonary (*n*)	16	15	31	
-Cerebral (*n*)	7	6	13	
Previous surgery [*n* (%)]	19 (17.0)	22 (22.2)	41 (19.4)	0.335
Alcohol [*n* (%)]	5 (4.5)	2 (2.0)	7 (3.3)	0.452[2]
Smoking [*n* (%)]	47 (42.0)	38 (38.4)	85 (40.3)	0.597
Previous pain [*n* (%)]	72 (64.3)	67 (67.7)	139 (65.9)	0.604
Previous bleeding [*n* (%)]	17 (15.2)	17 (17.2)	34 (26.1)	0.694
Hematemesis [*n* (%)]	77 (68.8)	69 (69.7)	146 (69.2)	0.882
Coagulopathy [*n* (%)]	4 (3.5)	3 (3.0)	7 (3.3)	0.917[2]
Hematocrit (%, Mean)	24.2 ± 3.2	23.6 ± 3.4	23.9 ± 3.1	0.567[1]
Index hematocrit < 25% (*n*)	47	45	92	0.610
Index hematocrit ⩾ 25% (*n*)	65	54	119	
Shock (*n*)	6	5	11	0.381[2]
Rockall score ⩽ 3 [*n* (%)]	63 (56.3)	52 (52.5)	115 (54.5)	0.737
> 8 [*n* (%)]	21 (18.7)	19 (19.1)	40 (18.9)	0.865

[1]Student's *t* test; [2]Fisher's exact test; NSAIDs: non-steroidal anti-inflammatory drugs.

Table 2 Clinical outcomes of the study population

Outcome	Group 1 (*iv*) (*n* = 112)	Group 2 (*po*) (*n* = 99)	Total (*n* = 211)	*P*
Inpatient basis				
Recovery [*n* (%)]	107 (95.5)	95 (96.0)	202 (95.7)	0.945
Re-bleeding [*n* (%)]	5 (4.5)	4 (4.0)	9 (4.3)	0.879[2]
Surgery requirement [*n* (%)]	3 (2.7)	2 (2.0)	5 (2.4)	0.773[2]
Hospital stay (days, mean)				
Total	4.6 ± 1.6	4.5 ± 2.6	4.5 ± 2.8	0.710[2]
⩽ 5 d (*n*)	52	55	107	0.093
> 5 d (*n*)	60	44	104	
Blood transfusion (units)				
Total (mean)	1.9 ± 1.1	2.1 ± 1.7	2.0 ± 1.6	0.350[1]
⩽ 3 units (*n*)	85	74	159	0.847
> 3 units (*n*)	27	25	52	0.610
Death [*n* (%)]	2 (1.8)	2 (2.0)	4 (1.9)	0.981[2]
Outpatient basis				
Re-bleeding [*n* (%)]	2 (1.8)	1 (1.0)	3 (1.4)	0.766[2]
Death [*n* (%)]	1 (0.8)	0 (0.0)	1 (0.4)	0.887[2]
Overall				
Re-bleeding [*n* (%)]	7 (6.2)	5 (5.0)	12 (5.6%)	0.745[2]
Death [*n* (%)]	3 (2.6)	2 (2.0)	5 (2.3)	0.980[2]

[1]Student's *t* test; [2]Fisher's exact test.

Table 3 Probable effects of variables on re-bleeding

Factor	Re-bleeding (*n*)	*P*	OR (95% CI)
Co-existing illness	5	0.288	2.3 (0.6-8.8)
Hematemesis	6	0.971	0.8 (0.2-3.6)
Smoking	5	0.490	1.9 (0.4-7.3)
Aspirin/NSAIDs	7	0.721	1.1 (0.3-8.7)
Age ⩾ 65 yr	5	0.117	2.1 (0.7-10.8)
Ulcer size > 1 cm	6	0.001	11 (2.6-46.3)
Ulcer locations:			
Posterior duodenal	4	0.041	7 (1.5-18.2)
Gastric corporal	3	0.049	5 (1.0-14.3)
Ulcer stigmata:			
Flat spots	5	0.001	12 (4.5-57.3)
Old clots	3	0.023	5 (1.2-13.5)

plus adrenal insufficiency in 1. Total hospital stay was 3 d at minimum and 20 d at maximum. The mean duration of hospital stay was 4.6 ± 1.6 d in Group 1 and 4.5 ± 2.6 d in Group 2. Length of hospital stay did not differ significantly between two groups ($P = 0.710$, Student's *t* test). Hospital stay more than 5 d was also similar between the groups ($P = 0.093$). The median number of units of blood transfused was approximately 2 in each group ($P = 0.350$, Student's *t* test). Blood transfusion requirement was more than 3 units in 27 (24.1%) patients of Group 1 and 25 (25.3%) patients of Group 2 ($P = 0.610$). Details about clinical outcomes are summarized in Table 2.

Bleeding from posterior duodenal (44.4%) and gastric corporal (33.3%) sites was more common compared to other sites [$P = 0.041$, OR 7 (1.5-18.2) and $P = 0.049$, OR 5 (1.0-14.3), 95% CI], respectively]. Of ulcers with re-bleeding, a diameter greater than 1 cm had a higher risk [$P = 0.001$, OR 11.0 (2.6-46.3), 95% CI]. Ulcers with flat spots and old clots had also higher risks for re-bleeding. Co-existing illnesses, hematemesis, smoking habit, aspirin/NSAIDs use and age older than 65 years did not have any effect on re-bleeding rates. The risk estimates of cofactors and their powers are summarized in Table 3.

Clinical outcomes after discharge in 30 d (outpatient basis)

We strictly informed patients or their relatives that it was very important to report to us any problems (new bleeding attack or death) immediately that occurred during the discharge period. None of the patients took aspirin or NSAIDs during the 30 d follow-up period. Four patients (or a relative) re-contacted us within 30 d. A new bleeding occurred in 2 patients of Group 1 and in 1 patient of

Group 2 after the index bleeding episode. The overall re-bleeding was seen in 12 (5.6%) patients [7 (6.2%) in Group 1 and 5 (5.0%) in Group 2]. Additionally, one patient died from Group 1 due to a new cerebrovascular event. Hence, the overall death was seen in 5 (2.3%) patients.

DISCUSSION

In the present study, we demonstrated that oral omeprazole was as effective as intravenous omeprazole in controlling bleeding peptic ulcers without high-risk stigmata. Importantly, the study implies that treatment with the oral agent is indicated for the bleeding instead of the *iv* approach when in reality, PPI use in this situation is simply to heal the ulcer. Although most of bleeding episodes from peptic ulcers resolve spontaneously and are not detrimental, recurrence of bleeding adversely affects prognosis. The overall re-bleeding rate in the oral treatment group (5.0%) was similar to that in the intravenous treatment group (6.2%) within 30 d, and both groups were also similar with respect to the need for surgery, duration of hospitalization, total amounts of blood transfusion, and mortality. Although clean base ulcers form the largest portion of the study population, the calculated Rockall scores were higher than 8 in approximately one fifth of the patients. As well-known, a score of higher than 8 is associated with a high risk of death[22]. Comorbidity and age were the predominant contributors to these high scores in our population.

Although the Federal Drug Administration has not approved intravenous proton pump inhibitors for the treatment of UGI bleeding, these agents are being used widely all around the world. A meta-analysis pointed out that PPI therapy in UGI bleeding was effective only in patients with UGI bleeding caused by peptic ulcers and with high-risk stigmata for re-bleeding[16]. Moreover, it has been reported that patients with endoscopy results showing a low risk of re-bleeding should not be treated endoscopically as their prognosis is excellent when treated conservatively[1].

What about oral versus intravenous drug administration? Most of the previous studies on omeprazole have been conducted with intravenous omeprazole and not with the oral drug. The oral absorption of omeprazole is 50%; however, as gastric pH rises, as much as 75% may be absorbed. It is highly protein-bound in plasma and is rapidly metabolized in the liver, and the metabolites are excreted in urine. The onset of antisecretory effect occurs within 1 h, with peak effects occurring in 2 h, depending on the dose[23]. Demonstration of effectiveness of oral treatment would be particularly attractive as it would allow treatment to be initiated outside, prior to hospital admission. However, it was concluded that pharmacotherapy alone could not replace endoscopic hemostasis for patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels[12]. On the other hand, it was reported that oral omeprazole therapy can be a valid alternative to endoscopic therapy, especially when injection therapy is not readily available[11]. Replacement of endoscopy in bleeding may be more possible in ulcers with low risk stigmata. Interestingly, one meta-analysis warned readers that those patients with UGI bleeding with significant comorbid diseases (such as diabetes mellitus, collagen vascular disease and hypercoagulable states) need careful monitoring, as intravenous PPI therapy in such patients may be harmful. Besides, all-cause deaths and non-ulcer deaths in trials using intravenous PPI were higher in the treatment group and not in trials using oral PPI[16].

The role of oral omeprazole in bleeding peptic ulcers was studied, especially in ulcers with high-risk stigmata by some authors and they found the rebleeding rates of omeprazole groups to be 7%, 10.9%, 15%, 22.9% and 26%, respectively[11,18,19,24,25]. Bour *et al*[25], Khuroo *et al*[19] and Jung *et al*[11] did not perform endoscopic therapy in omeprazole groups, while Javid *et al*[24] and Kaviani *et al*[18] did so. Jung *et al*[11] reported that oral omeprazole administration was comparable to endoscopic ethanol injection therapy for prevention of re-bleeding in patients with nonbleeding visible vessels or adherent clots. Moreover, Kaviani *et al*[18] showed that oral omeprazole reduced the re-bleeding rate, hospital stay and need for blood transfusion even in high-risk ulcers after endoscopic therapy. Khuroo *et al* reported a lower re-bleeding rate with oral omeprazole alone compared to placebo[19], which is comparable to the re-bleeding rates achieved by endoscopic therapy alone[13,14]. Bour *et al* also reported that oral omeprazole was comparable to endoscopic injection therapy[25], but they administered a smaller dose of omeprazole (40 mg every 24 h) than we did. This dosage may not be sufficient to maintain intragastric pH > 4. Detailed studies *in vitro* have shown that at a pH of < 6, the extrinsic and intrinsic coagulation cascades are impaired, and platelet aggregation is virtually abolished[26]. In our study, omeprazole at a dose of 40 mg every 12 h was administered because the gastric pH was reported to be > 6 during 85% of the first 24 h period at that dose[19].

Although it was declared four years ago by the British Society of Gastroenterology Endoscopy Committee[1] that patients who have active bleeding from the ulcer, a non-bleeding visible vessel, or have adherent clots should be recommended to receive endoscopic therapy (grade A), it was subjected to strong objections[27] and the disapproval was supported by a meta-analysis[15]. After a clot has been diagnosed, approaches to its management are quite different. Removal of blood clots is probably more hazardous in centers where clinicians are less experienced in handling peptic ulcer bleeding. However, targeted irrigation has been shown repeatedly to be safe and should be widely adopted in managing ulcers with adherent clots[28]. Randomized, controlled trials of endoscopic therapy versus non endoscopic therapy for ulcers with adherent clots have yielded conflicting results[13,29], and a meta-analysis does not support routine use of endoscopic therapy[15]. Our study groups had a low count (10 *vs* 11) of adherent clots and they had a lower risk for re-bleeding. The risk for re-bleeding with clots that remained adherent after washing has been reported to be only 8%[30]. We repeated the analysis excluding clots and found out that re-bleeding rates were also similar in both groups. On the other hand, the rebleeding rate of 10.8% (5/46) in the flat spot group is higher compared with other studies[4]. Interobserver variability of stigmata classification could be

a major limitation in this condition.

H pylori infection and chronic aspirin/NSAID use are the two major risk factors among patients hospitalized for ulcer bleeding[17]. Eradication of *H pylori* has been demonstrated in many randomized, controlled trials[31,32], to reduce the rate of ulcer recurrences and rebleeding in complicated ulcer diseases. In a recent study, duodenal ulcers were more likely to be associated with *H pylori* infection than gastric ulcers. In contrast, gastric ulcers were more likely associated with aspirin/NSAID use than were duodenal ulcers[17]. In patients with upper gastrointestinal bleeding, the sensitivity of the rapid urease test is relatively low in detecting *H pylori*. It was reported that this was best accomplished by histologic examination with a sensitivity above 90%[33], and therefore we did so. In our study, *H pylori* infection was present in 98 (61.2%) patients with duodenal ulcer, and in 21 (41.2%) patients with gastric ulcer ($P = 0.012$). Aspirin/NSAID use was seen in 82% of gastric ulcers, while in 62% of duodenal ulcers ($P = 0.007$). It was also reported that prior use of aspirin/NSAIDs increases the risk of re-bleeding in bleeding ulcer patients, and leads to a higher need for urgent surgery[34]. In parallel with this conclusion, surgery requirement was mostly seen in patients taking aspirin/NSAIDs in both groups (2, for each) in our study. On the other hand, endoscopic features of high-risk included ulcer size (> 1 or 2 cm)[34,35] and the site of bleeding (the posterior lesser gastric curvature and posterior duodenal wall)[36-38]. Bleeding from posterior duodenal (44.4%) and gastric corporal (33.3%) ulcers was more common compared to other sites in our study (Table 3). The mean age of our study population was 52 years, and more than one third had co-existing illnesses.

In conclusion, our results suggest that the effectiveness of oral omeprazole administration is comparable to intravenous therapy in terms of re-bleeding, need for emergency surgery, transfusion requirements, length of hospital stay and mortality in patients with bleeding peptic ulcers without high risk stigmata. In most of the countries, most patients with bleeding ulcers have low risk stigmata, and thus, can be treated with oral omeprazole. These patients do not explicitly require expensive omeprazole infusions.

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COMMENTS

Background

As yet, there is no study in the literature that had a head-to-head comparison of oral *vs* intravenous proton pump inhibitor treatment in bleeding peptic ulcers. We designed a study to compare the effect of *iv* and *po* omeprazole in patients with bleeding peptic ulcers without high-risk stigmata.

Research frontiers

We demonstrate that the effect of oral omeprazole is as effective as intravenous therapy in terms of re-bleeding, surgery, transfusion requirements, hospitalization and mortality in patients with bleeding ulcers with low risk stigmata. These patients can be treated effectively with oral omeprazole.

Innovations and breakthroughs

Our results suggest that the effectiveness of oral omeprazole administration is comparable to intravenous therapy in terms of re-bleeding, need for emergency surgery, transfusion requirements, length of hospital stay and mortality in patients with bleeding peptic ulcers without high risk stigmata. Generally speaking, most patients with ulcer bleeding have low-risk stigmata, and thus, can be treated with oral omeprazole. These patients do not explicitly require expensive omeprazole infusions.

Peer review

It is a practical research to compare the effectiveness of oral omeprazole *vs iv* omeprazole in peptic bleeding cases without high risk stigmata. The results showed that oral treatment is as effective as the iv treatment but less expensive. The study was well designed with enough material as well as statistical analysis.

S- Editor Liu Y **L- Editor** Zhu LH **E- Editor** Liu WF