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**ORIGINAL ARTICLE**

# Erythromycin decreases the time and improves the quality of EGD in patients with acute upper GI bleeding

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## ABSTRACT

**Aim**: To evaluate the efficacy of erythromycin to decrease the time and improves the quality of EGD in patients with acute upper GI bleeding.

**Background**: The diagnostic and therapeutic value of esophagogastroduodenoscopy (EGD) in patients with upper GI bleeding is often limited by the presence of residual blood or clots. Infused erythromycin (3 mg/kg) before EGD, a potent gastro kinetic drug, might improve the quality of EGD in patients with upper GI bleeding and decrease the time of EGD and second- look EGD.

**Patients and Methods**: In a prospective, randomized, double-blind controlled trial, 40 patients with acute upper gastrointestinal bleeding in Taleghani hospital, Tehran, Iran were studied. The patients were randomized into 2 groups: 1) nasogastric tube placement receiving placebo, and 2) intravenous erythromycin infusion (3mg/kg at 30 min) combined with nasogastric tube placement. The primary end point was endoscopic yield, as assessed by objective and subjective scoring systems and endoscopic duration. Secondary end points were the need for a second look, blood units transfused, and length of hospital stay and mortality.

**Results**: A clear stomach was found more often in the erythromycin group (100% vs. 25%; $P< 0.001$). Erythromycin shortened the endoscopic duration (14 vs. 32 minutes in the placebo group; $P< 0.001$) and reduced the need for second-look endoscopy (1 vs. 3*;* $P< 0.001$), admission duration (2 vs 5; $P< 0.001$) and reduced the blood units transfused (2 vs 4*;* $P< 0.001$).

**Conclusion**: In patients with acute upper GI bleeding, infusion of erythromycin before endoscopy significantly decreases the time and improves the quality of EGD.

**Keywords**: Erythromycin, Upper gastroinestinal bleeding, Esophagogastroduodenoscopy.

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## Introduction

The annual incidence of hospital admission for upper GIB (UGIB) in the United States and Europe is 0.1%, with a mortality rate of 5–10%. Patients rarely die from exsanguination; rather, they die due to decompensation from other underlying illnesses. Independent predictors of re-bleeding and death in patients hospitalized with UGIB include higher age, co-morbidities, and hemodynamic compromise (tachycardia or hypotension) (1). Acute upper GI bleeding (UGIB), a common cause of emergent

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hospitalization, is associated with significant morbidity and mortality. The diagnostic and therapeutic value of esophagogastroduodenoscopy (EGD) among these patients is well established (2, 3). Moreover, available data suggest that EGD early in the clinical course is safe and effective (4). However, in patients with active or recent hemorrhage, the quality of the examination can be limited by the presence of residual blood and clots in the upper GI tract, especially in the gastric fundus (5).

To avoid this problem, gastric lavage is usually performed by using a large-diameter nasogastric tube just before EGD. When blood or clot persist in the stomach despite this manoeuvre, further lavage can be performed by using a water pump during endoscopy and the patient can also be turned to move blood and clots to other parts of the stomach. Other proposed manoeuvres include vigorous gastric lavage by means of a nasogastric tube during EGD (6). The use of an endoscope with large diameter accessory channel (7-9) and instillation of 3% hydrogen peroxide to dissolve small clots and render blood translucent (10). Nevertheless, failure to identify the cause of bleeding at the initial EGD often necessitates a second EGD (second-look) within several hours with a resultant delay in diagnosis that can increase morbidity and mortality (5).

Erythromycin, a macrolide antibiotic discovered in 1952, is a major motilin receptor agonist that accelerates gastric emptying by inducing antral contractions similar to phase III of the interdigestive migrating motor complex (11-15). Coffin B et al. revealed that infusion of erythromycin before emergency endoscopy can give better visualization in EGD and decrease the need for re- endoscopy (16).This study was designed to evaluate the effect of erythromycin on EGD among patients suffering from upper GI bleeding.

## Patients and Methods

A prospective, randomized, double blind, controlled trial was conducted. All patients with hematemesis and melena admitted to Taleghani hospital were included if they met the following criteria: age over 18 years; upper GI bleeding, defined as either fresh and bright red hematemesis or coffee ground hematemesis and admission within 12 hours of the initial signs of bleeding. All patients who were admitted underwent upper GI endoscopy when they were hemodynamically stable, with heart rate less than 100 beats/min and systolic pressure greater than 100 mm Hg at the time of endoscopy. The exclusion criteria were known allergy to erythromycin or to other macrolides, encephalopathy, not giving informed consent, concomitant terfenadine, astemizole or cyclosporin use because of possible interactions with erythromycin, prior gastrectomy, and pregnancy or lactation. After getting informed consent, eligible patients were randomly assigned to erythromycin or placebo. As part of the clinical evaluation, a 16F to 20F polyvinyl nasogastric tube was positioned in the stomach and a gastric lavage with water was performed to determine whether blood, red or black, was present (defined as a positive gastric lavage), and whether the lavage was positive to attempt to clear blood from the stomach. The volume of water used for lavage was not quantified. After inclusion, placebo or erythromycin (3mg/kg) was mixed with 100 mL of isotonic saline solution before infusion and was administered intravenously over 5 minutes. Thirty to 60 minutes thereafter, emergency endoscopy was performed with the patient in the left lateral position by using lidocaine pharyngeal anesthesia. No other drug was used on a regular basis. Each procedure was timed from start to finish.

Endoscopies were performed by a senior Fellowship candidate of gastroenterology and 2 members of the regular endoscopic team that performs emergent EGD. Before starting the

study, the methodology and grading scales were presented and discussed during a special meeting to ensure that these were understood by all members of the team. After completion of the EGD, the results were noted by using the standardized reporting method. The quality of visualization of the esophagogastroduodenal tract was immediately evaluated using a scale of 0 to 3: 0, insufficient preparation with large volume of red or black blood and/or adherent clots that could not be removed by lavage performed through the accessory channel of the endoscope; 1, poor preparation with a moderate volume of red or black blood and/or clots that could be fully removed during the examination by active lavage through the accessory channel; 2, good preparation with a small volume of red or black blood, but no clots; and 3, excellent preparation without blood or clots. The need for a second EGD, number of paced cell after EGD, duration of admission, using clips or injection, and patients outcome were also noted. Adverse events were recorded.

The project was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Data were presented as mean± standard deviation for numerical variables and frequency (percent) for categorical data. Quality of EGD, measured by a subjective scale (0-3) and the need for re-endoscopy were the outcome variables of our study. Data were analyzed using chi- square and t- test and SPSS software version 16. $P< 0.05$ was considered as significant.

## Results

Forty patients (22 male, 18 female) admitted to emergency ward for UGIB were included in the study; 20 were randomized to receive erythromycin before EGD and 20 received placebo. Patients' characteristics, hemoglobin on admission, and number of units of blood transfused before EGD did not differ significantly between the 2 groups (Table 1). The groups were similar in sex (11 male and 9 female in each group), age (62 ± 17 vs 62 ± 17 years), delay between onset of bleeding and endoscopy, systolic blood pressure, and heart rate. The haemoglobin level before EGD was not significantly different in the 2 groups. Thirty- eight patients presented with hematemesis and 2 patients with melena. Three patients had cirrhosis (2 in erythromycin group and 1 in placebo).

Gastric lavage was positive in 19 patients in each group except 1 patient in each group. Quality of the EGD examination was significantly better in patients who received erythromycin than in the control patients (20 vs 3; $p<0.001$). In addition, the mean duration of the endoscopic procedure was shorter in the erythromycin group (13.6 ± 2.7 vs 31.7 ± 6.1; $p<0.001$).

A second EGD was required within 5 days in 1 patient in the erythromycin group versus 3 patients in the control group ($p<0.001$). A second EGD was performed significantly more often in patients with poor preparation ($p<0.001$). Median (range) duration of hospitalization tended to be shorter for patients in the erythromycin group (2 days [3±1 days]) compared with those in the control group (5 days [5±2 days]); the difference was significant ($p<0.001$). The blood units transfused within 24 hours after the initial endoscopy were less in erythromycin group than in placebo group (1±1 vs 5±2 units; $p<0.001$). The need for injection or clips was not different between the 2 groups ($p>0.99$). Only 1 death occurred within the first 48 hours after the endoscopic procedure in control group but the difference was not significant ($p>0.99$). No complication was reported throughout the study (table 2).

## Discussion

This study was designed to determine the effects of intravenous erythromycin infusion on

**Table 1.** Patients' characteristics before EGD

| | | Total | Placebo | Erythromycin | P-value |
|---|---|---|---|---|---|
| Age | | 61 ± 16* | 62 ± 17 | 61 ± 15 | 0.64 |
| | | 66 (22-88)† | 68 (22-88) | 65 (39-85) | |
| Sex | Male | 22 (55)‡ | 11 (55) | 11 (55) | 1 |
| | Female | 18 (45) | 9 (45) | 9 (45) | |
| Hemoglobin Baseline | | 8.9 ± 1.9 | 8.3 ± 2.1 | 9.4 ± 1.7 | 0.081 |
| | | 8.8 (5.1-12.4) | 8.1 (5.1-12.4) | 9.5 (6-12) | |
| Hemoglobin Pre-endoscopy | | 8.2 ± 1.6 | 7.7 ± 1.4 | 8.8 ± 1.7 | 0.04 |
| | | 8 (5.3-12) | 7.7 (5.3-10) | 8.8 (5.8-12) | |
| Hematemesis | No | 2 (5) | 1 (5) | 1 (5) | 1 |
| | Yes | 38 (95) | 19 (95) | 19 (95) | |
| Melena | No | 20 (50) | 11 (55) | 9 (45) | 0.527 |
| | Yes | 20 (50) | 9 (45) | 11 (55) | |
| Anemia | No | 2 (5) | 1 (5) | 1 (5) | 1 |
| | Yes | 38 (95) | 19 (95) | 19 (95) | |
| Cirrhosis | No | 14 (82.4) | 6 (85.7) | 8 (80) | >0.99 |
| | Yes | 3 (17.6) | 1 (14.3) | 2 (20) | |
| Renal Failure | No | 40 (100) | 20 (100) | 20 (100) | 1 |
| | Yes | 0 | 0 | 0 | |

* Mean ± standard deviation; † Median (range); ‡ Frequency (%)

**Table 2.** Characteristics of EGD, intervention and re-endoscopy

| | | Total | Placebo | Erythromycin | P-value |
|---|---|---|---|---|---|
| Pack cell after endoscopy | | 3 ± 2* | 5 ± 2 | 1 ± 1 | <0.001 |
| | | 3 (0-10) | 4 (2-10) | 2 (0-5) | |
| Endoscopy Status | Good | 25 (62.5) | 5 (25) | 20 (100) | <0.001 |
| | Not good | 15 (37.5) | 15 (75) | 0 | |
| Endoscopy Number | | 2 ± 0.7 | 2.5 ± 0.5 | 1.5 ± 0.5 | <0.001 |
| | | 2 (1-3) | 2.5 (2-3) | 1 (1-2) | |
| | 1 | 11 (27.5) | 0 | 11 (55) | |
| | 2 | 19 (47.5) | 10 (50) | 9 (45) | |
| | 3 | 10 (25) | 10 (50) | 0 | |
| Addmission Duration | | 4 ± 2 | 5 ± 2 | 3 ± 1 | <0.001 |
| | | 4 (1-10) | 5 (1-10) | 2 (1-5) | |
| Injection | No | 31 (77.5) | 16 (80) | 15 (75) | >0.99 |
| | Yes | 9 (22.5) | 4 (20) | 5 (25) | |
| Clips | No | 36 (92.3) | 18 (90) | 18 (94.7) | >0.99 |
| | Yes | 3 (7.7) | 2 (10) | 1 (5.3) | |
| Outcome | Discharge | 39 (97.5) | 19 (95) | 20 (100) | >0.99 |
| | Expired | 1 (2.5) | 1 (5) | 0 | |
| Time of endoscopy | | 22.7 ± 10.3 | 31.7 ± 6.1 | 13.6 ± 2.7 | <0.001 |
| | | 18 (9-40) | 32.5 (15-40) | 14 (9-18) | |

* Mean± standard deviation; Median (range); ‡ Frequency (%)

emergency endoscopic yield, time of the endoscopy and the outcome in patients with recent hematemesis. EGD is now widely accepted as a standard for the management of patients with acute UGIB because it results in early recognition of the cause of bleeding, leading thereby to appropriate and immediate treatment (17). When a large volume of blood is present, EGD may be feasible but it requires more time and experience and is often poorly tolerated by patients. The risk of vomiting during the procedure is also increased with the possibility of aspiration and pulmonary complications. The frequency with which the persistence of blood and/or clots is noted in the

stomach during EGD in patients with UGIB varies from 5.6%, as found in a survey of members of the American Society for Gastrointestinal Endoscopy, to 23% of patients (18- 21). Among prokinetic drugs, erythromycin, when given intravenously at a dose of 3 mg/kg, has the most powerful effects on gastric clearance. This has been established in healthy subjects as well as in patients with diabetic gastroparesis and critically ill patients (22, 23). As a motilin agonist, erythromycin stimulates antral contractions similar to phase III of the interdigestive migrating motor complex (24).

This study showed that infusion of erythromycin before emergency EGD improved the quality of EGD and gave better visualization for endoscopists. It is similar with results of two studies performed by Coffin B et al. and Frossard JL, et al. in which they observed better visualization of the field of endoscopy among patients with upper GI bleeding (16, 25). Meanwhile, Pateron et al. showed that visualization of endoscopic field was not influenced by the technique of preparation, such as NG tube placement or erythromycin infusion. However they observed the advantage of the combination of erythromycin and lavage in highly severe events (26).

The present study revealed the significant benefit of erythromycin in reducing the need of re-endoscopy, hospital stay, and blood transfusion. Moreover, Emergent EGD has decreased morbidity, mortality and cost among these patients (27).Preserved clot in the fundus may lead to missed lesion up to 41% of the patients (5). Missed lesions are related with high morbidity and mortality, increased hospital stay (28,*29*).Advantages of prescribing erythromycin before emergent EGD on the morbidity and mortality have been proved in other clinical trials(16, 25, 30). Moreover, these useful effects of erythromycin on reducing re- endoscopies and morbidity and mortality can result in cost saving and increase in QALY. Winstead et al. assessed the cost-effectiveness of erythromycin before EGD. They found that infusion of erythromycin prior to EGD resulted in a cost-effective outcome in a majority of trials using willingness-to-pay figures of USD 0, USD 50,000 and USD 100,000 per quality-adjusted life-year (QALY) (31).

This clinical trial showed that a single infusion of erythromycin, 3 mg/kg, significantly improved the quality of the EGD in patients suffering from upper GI bleeding. It is shown that erythromycin has not restricted the operation of EGD or hemostatic procedures (16).We used a subjective scale for measuring visualization of EGD field. This scale has been assessed and verified in another study (16). It may be associated with some biases. Moreover, the number of patients in this trial was too small to demonstrate a significant improvement. But, other findings, such as reduced need for a second endoscopy, reduced hospital stay, less need of blood transfusion, and also low side effects, as well as increased cost-effectiveness are in favour of prescribing erythromycin in patients with acute upper GI bleeding. To further establish the benefit of erythromycin in patients with UGIB, controlled studies with larger numbers of patients are recommended.

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