Original Article

Administration of Erythromycin Before Endoscopy in Upper Gastrointestinal Bleeding: A Meta-analysis of Randomized Controlled Trials

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See accompanying editorial on page 193

ABSTRACT

Background/Aim: Erythromycin infusion before endoscopy in upper gastrointestinal bleeding (UGIB) has been hypothesized to aid in visualization and reduce the need for second-look endoscopy; however, the results have been controversial. To evaluate further, we performed a meta-analysis comparing the efficacy of erythromycin infusion before endoscopy in acute UGIB. **Methods:** Multiple databases were searched (March 2013). Only randomized controlled trials were included in the analysis. A meta-analysis for the effect of erythromycin or no erythromycin before endoscopy in UGIB were analyzed by calculating pooled estimates of primary (visualization of gastric mucosa and need for second endoscopy) and secondary (units of blood transfused, length of hospital stay, duration of the procedure) outcomes. Statistical analysis was performed using RevMan 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). **Results:** Six studies (N = 558) met the inclusion criteria. Erythromycin infusion before endoscopy in UGIB demonstrated a statistically significant improvement in visualization of the gastric mucosa [odds ratio (OR) 3.43; 95% confidence interval (CI): 1.81 to 6.50, $P < 0.01$] compared with no erythromycin. In addition, erythromycin infusion before endoscopy resulted in a statistically significant decrease in the need for a second endoscopy (OR 0.47; 95% CI: 0.26 to 0.83, $P = 0.01$), units of blood transfused (WMD − 0.41; 95% CI: −0.82 to −0.01, $P = 0.04$), and the duration of hospital stay (WMD − 1.51; 95% CI: −2.45 to −0.56, $P < 0.01$). **Conclusions:** Erythromycin infusion before endoscopy in patients with UGIB significantly improves visualization of gastric mucosa while decreasing the need for a second endoscopy, units of blood transfused, and duration of hospital stay.

Key Words: Erythromycin, endoscopy, meta-analysis, upper gastrointestinal bleeding

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Upper gastrointestinal bleeding (UGIB) is a common medical emergency that accounts for more than 500,000 hospital admissions each year.[1] Despite advances in medical therapy, a significant mortality (5-10%) with severe upper gastrointestinal (GI) bleeding still exists.[2] Therefore, in the setting of UGIB, urgent endoscopy with adequate gastric mucosal visualization is pivotal for identification and treatment of bleeding lesions.

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Erythromycin, a macrolide antibiotic, facilitates the motility of the gastric antrum and duodenum by acting as a motilin receptor agonist.[3] Erythromycin, even in lower doses (70 mg), has been shown to accelerate gastric emptying.[4] Although various other modalities, including gastric lavage and metoclopramide, have been studied on gastric emptying, erythromycin may be more effective for enhancing gastric motility in UGIB.[5,6]

Various studies have been done for evaluating the effectiveness of erythromycin infusion before endoscopy to improve visibility and the therapeutic potential of endoscopy; however, the results have been controversial.[7-13] In addition, three meta-analyses have been performed examining the use of prokinetics with UGIB with varying results.[14-16] To evaluate further, we performed

a meta-analysis with multiple recent studies comparing the efficacy of erythromycin infusion before endoscopy in acute UGIB.

METHODS

A comprehensive literature search was performed using multiple databases, including PubMed/Medline, EMBASE, CINAHL, Scopus, Cochrane Databases, and abstracts from major conferences (DDW and ACG national meetings from 2003 to present) in March 2013 using search terms of erythromycin and bleeding, gastrointestinal hemorrhage, hemorrhage, and/or endoscopy. References of the retrieved articles and reviews were manually searched for any additional articles. Authors were contacted if data were missing or required clarification.

Only randomized controlled trials (RCTs) on adult patients that compared erythromycin infusion with no erythromycin infusion before endoscopy in adult patients with UGIB were included in the analysis with no language restrictions. If nasogastric lavage was utilized, only randomized trials that performed nasogastric lavage on both the groups (erythromycin and no erythromycin) were included. Two reviewers (MLB and ST) independently assessed the trials and extracted the appropriate data to be included in the analysis. Any disagreements were evaluated and settled by a third party (AC). The quality of studies were assessed using the Jadad scoring system (5 = excellent quality, 0 = poor quality).[17] The five criteria used in the scoring system are randomization, method of randomization being appropriate and described, double blinding, double blinding being appropriate and described, and description of withdrawal and drop outs.[17]

Meta-analysis for the effect of erythromycin or no erythromycin before endoscopy in UGIB were analyzed by calculating pooled estimates of primary (visualization of gastric mucosa and need for second endoscopy) and secondary (units of blood transfused, length of hospital stay, duration of the procedure) outcomes. The results were reported using odds ratio (OR) and weighted mean difference (WMD) with random effects model. Heterogeneity was analyzed by calculating the I^2 measure of inconsistency and was considered significant if $P < 0.10$ or $I^2 > 50\%$. If heterogeneity was statistically significant, a sensitivity analysis was utilized to examine for heterogeneity when certain studies were excluded from the analysis. Statistical analysis was performed using RevMan 5.1. Publication bias was assessed by funnel plots.

RESULTS

Article search and identification

Upon searching the multiple databases, 651 articles and abstracts were identified [Figure 1]. Upon review of titles and abstracts, 623 articles and abstracts were excluded due to not meeting the inclusion criteria for this meta-analysis. Of the remaining 28 articles and abstracts, seven RCTs from 2002 to 2011 were identified and included in the analysis (N = 558) with varying locations (Switzerland, Poland, Saudi Arabia, United States, and three studies from France).[7-13] The mean age ranged from 56 to 64.5. The details of the included studies are demonstrated in Table 1.

Visualization of the gastric mucosa

Visualization was evaluated by seven studies (N = 558).[7-13] Gastric mucosa was adequately visualized in 209 of 278 patients (75%) in the erythromycin group compared with 147 of 280 (53%) in the no erythromycin group. Erythromycin infusion before endoscopy in UGIB demonstrated a statistically significant improvement in visualization of the gastric mucosa [OR 3.43; 95% confidence interval (CI): 1.81 to 6.50, $P < 0.01$] as compared with no erythromycin [Figure 2]. Statistically significant heterogeneity was observed ($I^2 = 56\%$, $P = 0.03$). A sensitivity analysis was performed by removing one study and it demonstrated no change in the results (OR 2.38; 95% CI: 1.56 to 3.64, $P < 0.01$) with no heterogeneity ($I^2 = 24\%$, $P = 0.25$).

Second-look endoscopy

The need for second-look endoscopy was evaluated by seven

Table 1: Details of the studies included in meta-analysis and Jadad score

Author	Study type	Blinded	Location	Number of patients	Erythromycin dose	Erythromycin infusion time (min)	Postinfusion EGD start time (min)	Jadad score
Carbonell *et al*. 2004	RCT	Yes	France	99	250 mg	30	30	5
Frossard *et al*. 2002	RCT	Yes	Switzerland	105	250 mg	5	20	5
Coffin *et al*. 2002	RCT	Yes	France	41	3 mg/kg	30	30-90	3
Rudzki *et al*. 2006	RCT	No	Poland	24	4 mg/kg	9	30-90	3
Altraif *et al*. 2011	RCT	Yes	Saudi Arabia	90	125 mg	10	30	5
Pateron *et al*. 2011	RCT	No	France	169	250 mg	20	30	3
Habashi *et al*. 2007[a]	RCT	Yes	United States	30	NA	NA	NA	4

[a]Abstract publication, EGD: Esophagogastroduodenoscopy, NA: Information not available, RCT: Randomized controlled trial

studies ($N = 558$).[7-13] Second-look endoscopy was required only in 44 of 278 patients (16%) in the erythromycin group compared with 74 of 280 patients (26%) in the no erythromycin group. There was a statistically significant decrease in the need for second-look endoscopy in erythromycin group (OR 0.47; 95% CI: 0.26 to 0.83, $P = 0.01$) as compared with no erythromycin group [Figure 3]. The heterogeneity was not statistically significant ($I^2 = 33\%$, $P = 0.17$).

Blood transfusion

Five randomized trials were included in the analysis ($N = 504$).[7-11] A statistically significant decrease in the need for blood transfusion was identified with the erythromycin group (WMD − 0.41; 95% CI: −0.82 to −0.01, $P = 0.04$) as compared with the no erythromycin group [Table 2]. The heterogeneity was not statistically significant ($I^2 = 0\%$ $P = 0.85$).

Hospital stay

Erythromycin before UGIB also showed a statistically significant decrease in the duration of hospital stay (WMD − 1.51; 95% CI: −2.45 to −0.56, $P < 0.01$) compared with the no erythromycin group in four studies ($N = 335$)[7-10] [Table 2]. The heterogeneity was not statistically significant ($I^2 = 0\%$ $P = 0.47$).

Duration of procedure

The duration of the endoscopy between the erythromycin and no erythromycin group was not statistically significant (WMD − 1.36; 95% CI: −4.69 to 1.97; $P = 0.42$) based on four studies ($N = 463$)[7,9-11] [Table 2]. Statistically significant heterogeneity was observed ($I^2 = 76\%$, $P < 0.01$). A sensitivity analysis was performed and demonstrated no significant change in the results (OR 1.46; 95% CI: −0.76 to 3.68, $P = 0.20$) with no heterogeneity ($I^2 = 0\%$, $P = 0.67$).

Publication bias

No publication bias was noted for the outcomes in this meta-analysis based on funnel plots [Figure 4].

DISCUSSION

Acute UGIB is a life-threatening emergency with significant mortality and morbidity. Although incidence of UGIB has decreased in the last two decades, rebleeding still occurs in 7-16% despite endoscopic therapy, with associated mortality unchanged significantly over the past 10 years.[18] Therefore, after initial resuscitation, endoscopy with adequate gastric mucosal visualization is imperative for identification of bleeding source and treatment to prevent further episodes.

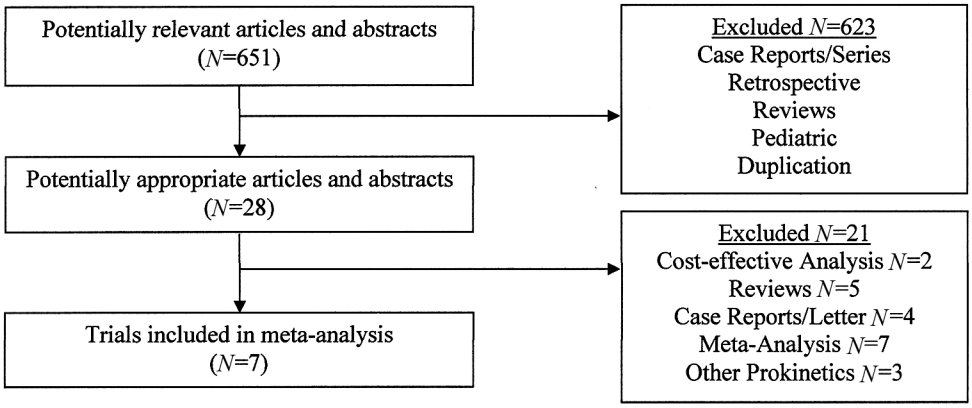

Figure 1: Article search algorithm in March 2013

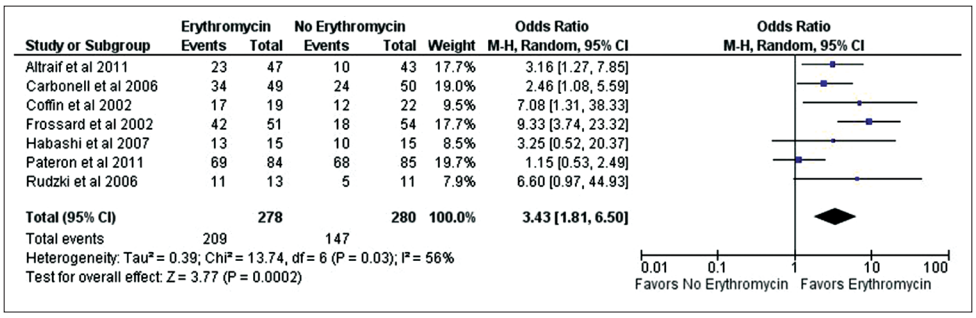

Figure 2: Forest plot demonstrating comparison for gastric visualization between erythromycin versus no erythromycin prior to endoscopy in patients with upper gastrointestinal bleeding

Table 2: Summary of the analyses performed between erythromycin versus no erythromycin prior to endoscopy for patients with upper gastrointestinal bleeding

Outcome	Weighted mean difference	95% Confidence interval	*P* value	I^2(%)
Units of blood transfused	−0.41	−0.82 to −0.01	0.04	0
Hospital stay	−1.51	−2.45 to −0.56	0.002	0
Duration of procedure	−1.36	−4.69 to 1.97	0.42	76

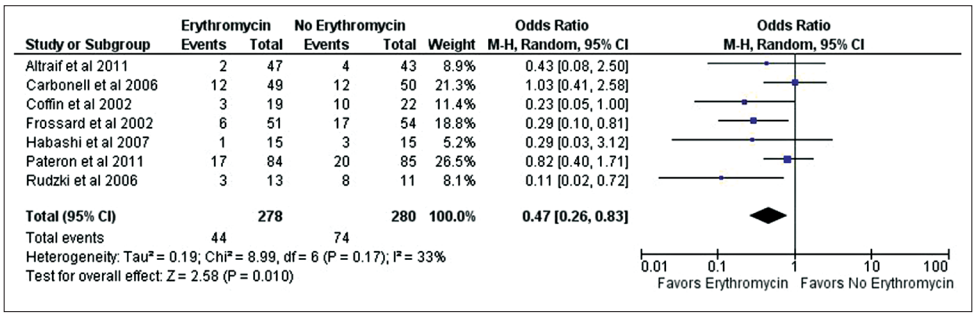

Figure 3: Forest plot demonstrating comparison for the need for second-look endoscopy between erythromycin versus no erythromycin prior to endoscopy in patients with upper gastrointestinal bleeding

The presence of blood clots in the stomach can impede good visualization of the gastric mucosa. Intravenous erythromycin appears to induce antral contractions similar to phase III of the interdigestive migrating motor complex.[19] It has also shown to improve tolerance of enteral feedings in critically ill patients better than other prokinetics, such as metoclopramide.[20] With these properties in mind, erythromycin has been studied in various RCTs for possible improvement in gastric visualization in patient with UGIB.

Over the past decade, RCTs evaluating erythromycin administration before endoscopy in patients with UGIB has been shown to improve gastric visualization in five RCTs.[7-10,12] However, Pateron *et al*. and Habashi *et al*., demonstrated no difference between those patients receiving erythromycin and those that do not.[11,13] Even more controversial, second-look endoscopy and duration of procedure were significantly reduced in only three studies[8,9,12] and two studies,[9,10] respectively. Similarly, hospital stay was significantly reduced in only one RCT.[10] The units of blood transfused was demonstrated to be nonsignificant between those receiving erythromycin and those with no erythromycin in five studies.[7-11] Given the variety of results among the RCTs, three meta-analyses were performed in the past two years.

Barkun *et al*., performed a meta-analysis in 2010 showing the use of prokinetics before endoscopy in patients with UGIB reduced the need for repeat endoscopy but did not reduce secondary parameters, such as hospital stay, units of blood transfused, or need for surgery.[14] However, this meta-analysis combined both erythromycin and metoclopramide. In 2011, two meta-analyses by Szary *et al*. and Bai *et al*., demonstrated that with erythromycin infusion before endoscopy in UGIB improved visualization while decreasing the need for second-look endoscopy, units of blood transfused, and length of hospital stay.[15,16] These meta-analyses included only four studies each and concentrated on erythromycin without metoclopramide. This suggests that metoclopramide may not be as effective as erythromycin in the gastric clearing of blood. Furthermore, Daram *et al*., also demonstrated that metoclopramide is inferior to erythromycin infusion before endoscopy for patients with UGIB.[21]

This meta-analysis, using new trials over the past two years, demonstrates that erythromycin given before endoscopy in UGIB results in statistically significant improvement in gastric visualization, while reducing need for second-look endoscopy, units of blood transfused, and hospital stay. This is the largest meta-analysis to-date, incorporating seven RCTs. Given these results, erythromycin before endoscopy in this population seems to be a reasonable treatment adjunct. As with any meta-analysis, strengths and weaknesses are present.

The strengths of our study are as follows. First, this meta-analysis included seven RCTs, making it the largest and most comprehensive meta-analysis to-date. Second, the populations varied among the studies, spanning five countries. Third, all studies were of adequate quality, based on Jadad score. Fourth, an aggressive article search was performed in which articles were included regardless of language. All trials were in English except one, which was in Polish and translated. Fifth, authors were contacted to clarify any data questions. Sixth, if statistically significant heterogeneity was observed, a random effects model was used and a sensitivity analysis was performed. The sensitivity

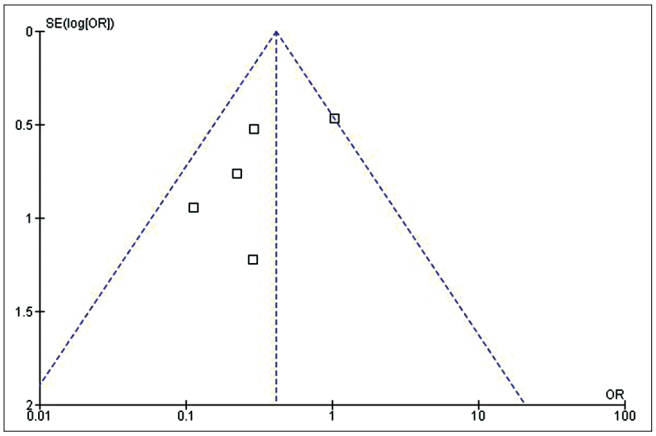

Figure 4: Funnel plot showing no publication bias

analysis was done by eliminating individual studies from the analysis if heterogeneity was observed. With this analysis, the demonstration of no statistically significant changes in the results without statistically significant heterogeneity enhances the validity of the results. Finally, this meta-analysis evaluated only erythromycin based on the possibility that metoclopramide may not be as effective, which has been our experience and experience of others.[6,21]

However, a few limitations to the study were observed. First, gastric visualization was based on endoscopists' judgment and varied slightly among studies. Therefore, gastric visualization was pooled as satisfactory versus unsatisfactory based on the individual trials definitions. Second, the dose of erythromycin varied slightly among the RCTs. Most studies used 250 mg erythromycin,[7,9,11] whereas other studies used 125 mg[10] and weight-based[8,12] erythromycin. The overall impact of these variations was minimal given the fact that weight-based erythromycin seems to correspond with ~250 and 125 mg of erythromycin demonstrated improved outcomes. In addition, erythromycin has been shown that even in doses as low as 70 mg can accelerate gastric emptying in critically ill patients.[4] Third, given the small number of patients in the studies, mortality could not be fully assessed in this meta-analysis. Further RCTs would be required to examine difference in mortality between the two groups. Fourth, statistically significant heterogeneity was observed for two outcomes (gastric visualization, procedure duration). However, upon sensitivity analysis, no changes in the results were observed without significant heterogeneity, enhancing overall validity of the results. Fifth, two of the studies utilized nasogastric lavage before administration of erythromycin.[7,11] However, data were utilized in which both groups (erythromycin and no erythromycin) received the same nasogastric lavage before procedure, minimizing any impact on the overall results. In addition, Guardiola *et al.*'s study was not included in the meta-analysis because the study compared nasogastric lavage with erythromycin without nasogastric lavage, which would have added the confounding variable of the nasogastric lavage.[22] Finally, two studies were not blinded,[11,12] which may introduce bias. However, a sensitivity analysis was performed in which both studies were removed and the results were similar for all measured outcomes, indicating little impact on overall results.

In conclusion, the administration of erythromycin before endoscopy in UGIB patients seems to improve visualization, while decreasing the need for second-look endoscopy, units of blood transfused, and hospital stay. Given the benefits in all primary and nearly all secondary outcomes, erythromycin should be strongly considered in patients presenting with UGIB before endoscopy.

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