Prokinetic therapy for feed intolerance in critical illness: One drug or two?

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Objective: **To compare the efficacy of combination therapy, with erythromycin and metoclopramide, to erythromycin alone in the treatment of feed intolerance in critically ill patients.**

Design: **Randomized, controlled, double-blind trial.**

Setting: **Mixed medical and surgical intensive care unit.**

Patients: **Seventy-five mechanically ventilated, medical patients with feed intolerance (gastric residual volume ≥250 mL).**

Interventions: **Patients received either combination therapy (n = 37; 200 mg of intravenous erythromycin twice daily + 10 mg of intravenous metoclopramide four times daily) or erythromycin alone (n = 38; 200 mg of intravenous erythromycin twice daily) in a prospective, randomized fashion. Gastric feeding was re-commenced and 6-hourly gastric aspirates performed. Patients were studied for 7 days. Successful feeding was defined as a gastric residual volume <250 mL with the feeding rate ≥40 mL/hr, over 7 days. Secondary outcomes included daily caloric intake, vomiting, postpyloric feeding, length of stay, and mortality.**

Measurements and Main Results: **Demographic data; use of inotropes, opioids, or benzodiazepines; and pretreatment gastric residual volume were similar between the two groups. The gastric residual volume was significantly lower after 24 hrs of treatment with combination therapy, compared with erythromycin alone (136 ± 23 mL vs. 293 ± 45 mL, *p* = .04). Over the 7 days, patients treated with combination therapy had greater feeding success, received more daily calories, and had a lower requirement for postpyloric feeding, compared with erythromycin alone. Tachyphylaxis occurred in both groups but was less with combination therapy. Sedation, higher pretreatment gastric residual volume, and hypoalbuminemia were significantly associated with a poor response. There was no difference in the length of hospital stay or mortality rate between the groups. Watery diarrhea was more common with combination therapy (20 of 37 vs. 10 of 38, *p* = .01) but was not associated with enteric infections, including *Clostridium difficile*.**

Conclusions: **In critically ill patients with feed intolerance, combination therapy with erythromycin and metoclopramide is more effective than erythromycin alone in improving the delivery of nasogastric nutrition and should be considered as the first-line treatment. (Crit Care Med 2007; 35:2561–2567)**

Key Words: enteral feeding; erythromycin; metoclopramide; nutrition; critical illness; prokinetic

Adequate enteral nutritional support is important in critical illness as it is cheaper, has fewer septic complications, and is associated with preservation of gut mucosal barrier function, compared with the parenteral route (1–6). However, slow gastric emptying and subsequent intolerance of nasogastric (NG) feeding occur in up to 50% of critically ill patients (1–3), compromising their nutritional status and increasing the risk of gastroesophageal reflux and aspiration (3–5), which adversely affect both morbidity and mortality (4–6).

Current therapeutic options for the management of feed intolerance in critically ill patients are prokinetic therapy, postpyloric feeding, or total parenteral nutrition (7–10). Of these, prokinetic agents, such as metoclopramide (a dopamine agonist) or erythromycin (a motilin agonist), are usually regarded as the first-line therapy (10–12). Metoclopramide has been reported to improve gastric emptying in critically ill patients (13–15), but its efficacy on the success of feeding in feed-intolerant patients remains controversial (14, 15). In small studies, a single dose of enterally administered metoclopramide had no effect on the gastric residual volume (GRV), and only modest reductions in volume were observed after three doses (14, 15). In contrast, low-dose (3–7 mg/kg/day) erythromycin increased both gastric emptying and the success of feeding in critically ill patients with feed intolerance (16–19). Comparative data among prokinetic agents have shown that enterally administered metoclopramide and cisapride may have a faster onset of action than erythromycin, but the impact of these drugs on the GRV in the critically ill is

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similar (15). Recently, intravenous (iv) erythromycin has been shown to be more effective than metoclopramide, but rapid tachyphylaxis develops with both drugs (20). In the patients who failed monotherapy, rescue combination therapy with erythromycin and metoclopramide was highly effective and tachyphylaxis was less prominent (20). Combination therapy may therefore be a better first-line approach to therapy; however, no data are available on the effectiveness of this strategy in the management of feed intolerance in the critically ill.

The primary aims of the current study were to compare the effectiveness of combination therapy against erythromycin alone as the first-line treatment for feed intolerance and to determine factors associated with resistance to treatment in critically ill patients. The impact of different prokinetic regimens on the following secondary outcomes was also examined: administered/prescribed caloric intake, incidence of vomiting, rate of postpyloric tube insertion and feeding, side effects, length of hospital stay, and mortality.

MATERIALS AND METHODS

Study Design. The study was conducted as a two-way randomized, double-blind, parallel-group study comparing the 7-day effectiveness of combination therapy with metoclopramide (10 mg iv four times daily) and erythromycin (200 mg iv twice daily) against erythromycin alone (200 mg iv erythromycin twice daily and four placebo injections of 0.9% normal saline for blinding purposes) in improving the success of NG feeding in feed-intolerant, critically ill patients. The study treatment was administered at 0400, 1000, 1600, and 2200 hrs.

Randomization of the study drugs was performed by a pharmacist using a computer-generated random number program and was concealed from the study investigators. After enrollment, the assigned therapy was prepared daily, placed in six 10-mL syringes, and placed into a black plastic bag by the dedicated pharmacist. Each syringe clearly stated the study number and time and date of administration; the latter of which was monitored by the principle investigator (NN) in a blinded fashion.

The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and run in accordance with the Australian National Health and Medical Research Committee Guidelines. Written informed consent was obtained from the patients' next of kin before enrollment.

Subjects. Seventy-five consecutive, mechanically ventilated patients who failed NG feeding were enrolled into the study from October 2005 to June 2006. Failure of feeding was defined as a GRV $\geq$250 mL $\geq$6 hrs after the commencement of feeding at a rate $\geq$40 mL/hr (Nutrison Standard: gluten and lactose free feed; 100 kcal, 4 g of protein, 12.3 g of carbohydrate, 3.9 g of fat per 100 mL; Nutricia N.V., Zoetermeer, The Netherlands). A 12-Fr (or larger) NG tube was placed into the stomach before the study, with the distal tip 10 cm below the gastroesophageal junction and clearly visible in the stomach on a routine abdominal radiograph. Radiologic confirmation of tube position was performed daily over the 7-day study period to ensure that the tube had not migrated into the duodenum.

Patients were excluded from the study if they 1) had received prokinetic drugs (metoclopramide, cisapride, or erythromycin) within the previous 24 hrs; 2) had a known allergy to a macrolide antibiotic or metoclopramide; 3) were receiving drugs known to interact with erythromycin (carbamazepine, cyclosporine, theophylline, aminophylline, digoxin, oral anticoagulants); 4) had undergone major gastrointestinal surgery (laparotomy with part of the gastrointestinal tract removed or repaired) within the previous 6 wks or had a past history of esophagectomy or partial or total gastrectomy; 5) were suspected of having bowel obstruction or perforation; 6) had evidence of liver dysfunction (i.e., >3 $\times$ elevation above the upper end of normal range of bilirubin, γ-glutamyl transferase, aspartate transaminase, alanine transaminase, or lactate dehydrogenase); or 7) had myasthenia gravis.

Protocol. At enrollment, enteral feeding was stopped temporarily and all gastric contents were manually aspirated with a 50-mL syringe. The GRVs obtained 6-hourly during the 24 hrs before the development of feed intolerance were recorded. Patients then received either combination or erythromycin alone therapy, in a randomized, double-blinded fashion as described. After the first dose of study medication, NG feeding was recommenced at a rate of 40 mL/hr. Manual aspiration of gastric contents was performed 2 hrs after administration of the first dose of therapy and then 6-hourly over the following 7 days. The rate of enteral feeding and the technique for NG aspirate collection followed the current standardized enteral feeding protocol in the Unit. If the subsequent 6-hourly GRV was <250 mL, the feeding rate was increased by 20 mL/hr every 6 hrs up to the patient's prescribed requirement rate (60–100 mL/hr). This was determined independently by a dietitian and was based on the patient's body mass index. In patients with a GRV <250 mL, the aspirated contents were returned via the NG tube. For aspirate volumes $\geq$250 mL, the contents were discarded and the rate of feeding was reduced by 50% or to a minimum of 20 mL/hr. If subsequent GRVs were <250 mL, aspirated contents were returned via the NG tube and the feeding rate was increased by 20 mL/hr every 6 hrs, up to patient's prescribed requirement rate.

Successful feeding was defined as the maintenance of a feeding rate $\geq$40 mL/hr with GRVs <250 mL (12, 16, 18, 20, 21). In these patients, the assigned therapy was continued for 7 days or until discharge. The adequacy of enteral nutrition or daily calorie intake was expressed as the administered/prescribed caloric ratio over 24 hrs duration. Failure of either therapy was defined as 1) two or more high GRVs (i.e., $\geq$250 mL) within the first 24 hrs; or 2) any 6-hourly GRV $\geq$250 mL thereafter while on $\geq$40 mL/hr of enteral feeding. In these patients, the study drugs were discontinued and enteral feeding was temporarily ceased. A postpyloric feeding tube was inserted endoscopically for patients who required ongoing nutritional support.

Data Collection and Analysis. Data on primary outcomes were collected prospectively over the 7 days of treatment: 6 hourly GRVs, amount of daily prescribed and administered feeds, occurrence of vomiting, and requirement for postpyloric feeding tube insertion. Secondary outcomes (length of hospital stay and mortality) and potential side effects of therapy (particularly the development of diarrhea) were also monitored up to 4 wks after the commencement of the therapy. Diarrhea was defined as frequent ($\geq$3/day) loose, liquid stool with an estimated total daily volume >250 mL (22). In all patients with diarrhea, stool specimens were evaluated for blood, white cells, bacteria, and parasites using microscopy, culture, and special stains. In addition, all specimens were tested for *Clostridium difficile* toxins (both A and B) using combination enzyme immunoassays (23).

Data are expressed as both intention to treat (ITT) and per protocol (PP) analyses. All enrolled patients (n = 75) were included in the ITT analysis, whereas only patients who participated in the trial for 7 days (n = 61) were included in the PP analysis.

Statistical Analysis. Based on our recent study (20), a difference in the rate of successful feeding between combination therapy and erythromycin alone was estimated to be approximately 40% (PP analysis). *A priori,* power calculations based on this difference indicated that $\geq$60 patients (30 patients in each arm) would be required for the PP analysis (i.e., patients who completed the 7 days) in order to demonstrate a statistically significant difference with an α value of <.05 and β value of 80%. In addition, as it was expected that not all enrolled patients would complete the 7-day study period, recruitment continued until $\geq$60 patients were included in the PP analysis. All statistical analyses were performed by an independent statistician. The study code was not broken until completion of the study.

Differences in demographic characteristics and severity of illness between the two groups were compared using the Student's unpaired *t*-test for continuous data and the Fisher's exact test for categorical data. Differences in the success of feeding over time were assessed using Kaplan-Meier survival curves with log-

rank test. Factors previously reported to be associated with a poor response to prokinetic therapy (20) were also compared by logistic regression analysis and Cox proportional hazards model. A two-way repeated measures analysis of variance with *post hoc* comparisons was used to compare the effect of the two treatments on the 1) GRV, 24 hrs before and after the commencement of therapy; and 2) administered/prescribed caloric ratio. Data are expressed as mean ± SEM. We considered $p < .05$ as statistically significant.

RESULTS

In the ITT analysis, 37 patients were randomized to combination therapy and 38 to erythromycin alone. The baseline details of patients, including demographics and admission illnesses, did not differ between the two groups (Table 1). Fourteen patients (seven combination and seven erythromycin alone) were excluded because their participation in the trial was ≤48 hrs. Reasons for early withdrawal of enteral feeding were recovery and ability to tolerate oral feeds (n = 9) and death after withdrawal of medical therapy (n = 5). Of the 61 patients who completed the 7 days (PP analysis), 30 received combination therapy and 31 patients received erythromycin alone. Patient demographics and characteristics included in the PP analysis were also similar between the two groups (Table 2).

GRVs Before and After 24 hrs of Treatment. On both ITT and PP analyses, GRVs decreased significantly after 24 hrs of treatment with both regimens (ITT and PP, $p < .0001$). The GRVs in patients treated with combination therapy were significantly smaller than those treated with erythromycin alone (ITT, $p = .034$; PP, $p = .02$) (Fig. 1).

Success of Gastric Feeding Over the 7 Days. On both ITT and PP analyses, combination therapy was associated with significantly greater feeding success than erythromycin alone, at all time points. Successful enteral feeding was achieved in almost all patients after 24 hrs of therapy. Over time, both treatments became less effective, with a marked reduction in the rate of successful feeding by day 7. Failure of therapy occurred earlier in patients treated with erythromycin alone (4.5 ± 0.5 days), compared with those treated with combination therapy (6.5 ± 0.5 days; $p = .003$) (Fig. 2).

Factors Associated With Poor Response. After we controlled for treatment effects, only sedation with opioid and/or benzodiazepines (relative risk, 3.30, con-

Table 1. Demographics and characteristics of critically ill patients included in intention-to-treat analysis

	Combination Therapy (n = 37)	Erythromycin Alone (n = 38)
Age, yrs, mean ± SEM	50.9 ± 3.4	52.1 ± 4.1
Gender, male/female	29:8	24:14
BMI, kg/m^2, mean ± SEM	27.2 ± 0.8	26.9 ± 1.0
Days in ICU prior to study, mean ± SEM	6.8 ± 1.2	5.0 ± 0.7
APACHE II score, mean ± SEM		
Admission	26.5 ± 1.0	26.2 ± 1.0
Study day	23.0 ± 0.9	22.6 ± 1.2
Enteral feeding rate before study, mL/hr, mean ± SEM	45 ± 2	41 ± 2
Days to intolerance	3.9 ± 0.8	3.0 ± 0.7
Diagnosis, n (%)[a]		
Sepsis	18 (47)	21 (55)
Respiratory failure	26 (70)	24 (63)
Trauma	11 (29)	10 (38)
Renal failure	3 (8)	7 (18)
Head injury	9 (24)	16 (42)
Burn	3 (8)	0
Diabetes mellitus	3 (8)	2 (5)
Blood glucose, mmol/L, mean ± SEM	8.4 ± 0.3	8.5 ± 0.3
Serum creatinine, mmol/L, mean ± SEM	0.098 ± 0.01	0.110 ± 0.02
Admission serum albumin, mmol/L, mean ± SEM	23.9 ± 0.9	23.7 ± 1.0
Medications, n (%)		
Opioid + benzodiazepine	28 (75)	28 (74)
Propofol	15 (41)	19 (50)
Inotropes	21 (56)	24 (63)
Insulin (Actrapid infusion)	26 (70)	29 (55)
Method of ventilation		
SIMV, n (%)	14 (38)	18 (47)
Pressure support, n (%)	23 (62)	20 (52)
Positive end-expiratory pressure, cm H_2O, mean ± SEM	8.6 ± 0.5	8.0 ± 0.7
Positive inspiratory pressure, cm H_2O, mean ± SEM	22.9 ± 1.4	23.3 ± 1.3

BMI, body mass index; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SIMV, synchronized, intermittent, mandatory ventilation.

[a]More than one diagnosis possible in any patient.

Table 2. Demographics and characteristics of critically ill patients included in per-protocol analysis

	Combination Therapy (n = 30)	Erythromycin Alone (n = 31)
Age, yrs, mean ± SEM	52.1 ± 2.1	49.9 ± 2.5
Gender, male/female	22:8	21:10
BMI, kg/m^2, mean ± SEM	27.5 ± 0.6	27.4 ± 0.7
Days in ICU prior to study, mean ± SEM	7.3 ± 1.0	5.0 ± 0.5
APACHE II score, mean ± SEM		
Admission	26.9 ± 0.7	26.1 ± 0.7
Study day	22.8 ± 0.5	22.7 ± 0.7
Enteral feeding rate before study, mL/hr, mean ± SEM	45 ± 2	41 ± 2
Days to intolerance, mean ± SEM	3.9 ± 0.8	3.0 ± 0.6
Diagnosis, n (%)[a]		
Sepsis	16 (53)	15 (48)
Respiratory failure	21 (70)	19 (61)
Trauma	8 (26)	8 (26)
Renal failure	3 (10)	6 (19)
Head injury	7 (23)	13 (42)
Diabetes mellitus	3 (10)	2 (6)
Blood glucose, mmol/L, mean ± SEM	8.3 ± 0.3	8.5 ± 0.2
Serum creatinine, mmol/L, mean ± SEM	0.092 ± 0.01	0.107 ± 0.01
Admission serum albumin, mmol/L, mean ± SEM	23.2 ± 0.9	23.7 ± 0.8
Medications, n (%)		
Opioid + benzodiazepine	22 (73)	22 (72)
Propofol	13 (41)	13 (40)
Inotropes	18 (60)	17 (58)
Insulin (Actrapid infusion)	20 (66)	22 (71)
Method of ventilation		
SIMV, n (%)	14 (46)	15 (48)
Pressure support, n (%)	16 (54)	16 (52)
Positive end-expiratory pressure, cm H_2O, mean ± SEM	8.7 ± 0.4	8.3 ± 0.5
Positive inspiratory pressure, cm H_2O, mean ± SEM	26.1 ± 1.0	24.2 ± 0.8

BMI, body mass index; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SIMV, synchronized, intermittent, mandatory ventilation.

[a]More than one diagnosis possible in any patient.

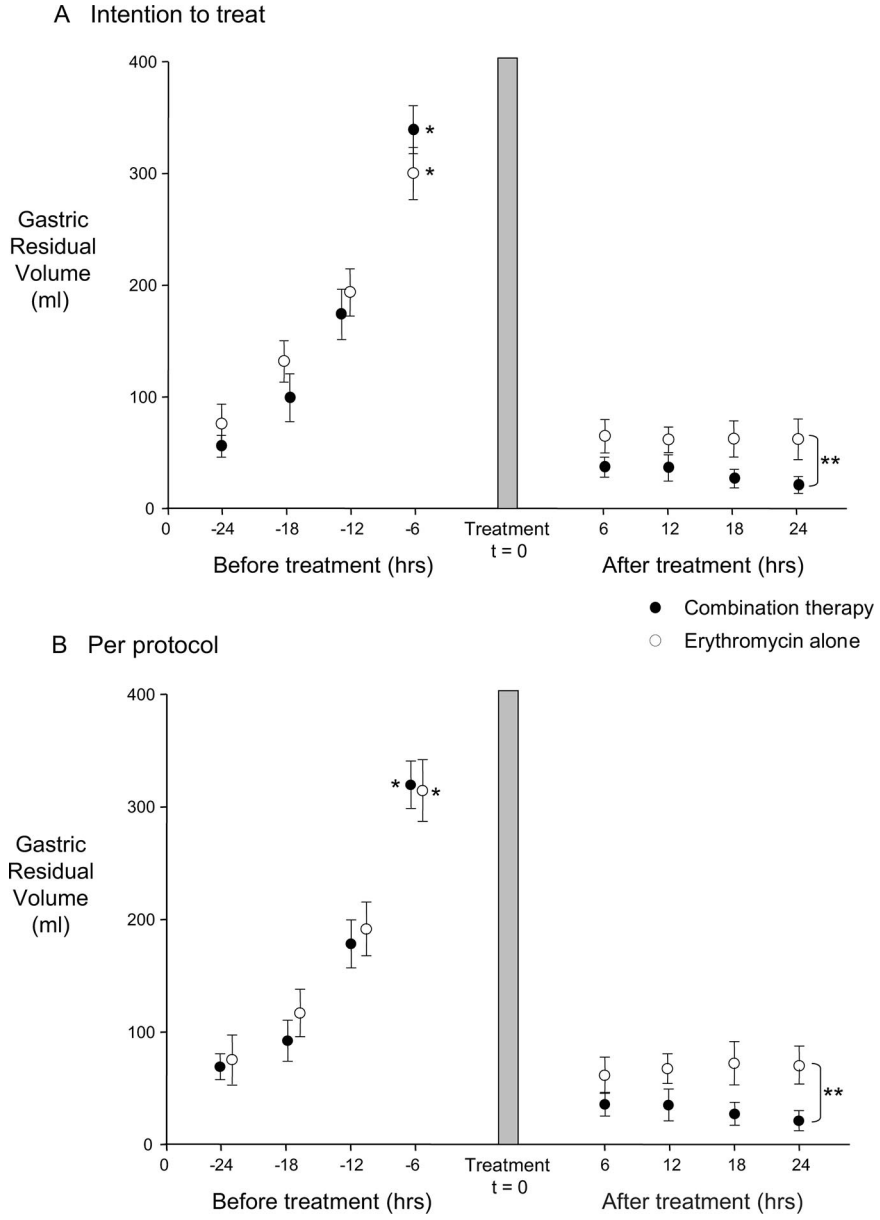

Figure 1. Six-hourly gastric residual volumes (GRVs) during the 24 hrs before (pretreatment) and after (day 1) the commencement of either combination therapy or erythromycin alone, based on intention to treat (*A*, including all enrolled patients, n = 75) and per-protocol (*B*, including only patients who completed all 7 days of the study, n = 61) analyses. *$p < .0001$, GRV 24 hrs before vs. after treatment with either combination or erythromycin-alone therapy; **$p < .05$, erythromycin vs. combination therapy 24 hrs after treatment.

fidence interval 1.30–8.20; $p = .01$), high pretreatment GRV (relative risk, 1.20, confidence interval 1.09–1.29; $p = .02$), and degree of hypo-albuminemia (relative risk, 1.10, confidence interval 1.03–1.19; $p = .01$) were significant predictors of a poor response to prokinetic therapy. Higher Acute Physiology and Chronic Health Evaluation II score was associated with a poor response on univariate analysis ($p = .01$) but not after controlling for treatment effects ($p = .18$).

Adequacy of Caloric Intake Over 7 Days. Over the 24 hrs before treatment, feed-intolerant patients received only one fourth of their prescribed calories. Both therapies significantly increased the amount of calories delivered, but the effect seemed to reduce over time, particularly in those treated with erythromycin alone. Overall, patients treated with combination therapy received a significantly greater proportion of their prescribed calories than those treated with erythromycin alone, based on both ITT ($p = .02$) and PP ($p < .001$) analyses (Fig. 3).

Secondary Outcomes. Based on both ITT and PP analyses, patients treated with combination therapy were less likely to require postpyloric tube insertion for ongoing enteral nutritional support, compared with those treated with erythromycin alone ($p = .04$). However, there were no differences in the rate of vomiting, length of hospital stay, or death in hospital between the groups (Table 3).

Side Effects of Prokinetic Therapy. During the 7-day treatment period, there were no reports of injection reactions, dystonic or dyskinetic movements, tremors, hypotension, or cardiac arrhythmia related to prolonged QT interval in either treatment group. Watery, loose, nonbloody bowel actions or diarrhea developed in 40% (30 of 75) of all patients, a mean of 13.8 ± 1.4 days after the commencement of therapy. Microbiological stool examination, however, was negative for inflammatory cells, *C. difficile* toxin, and bacterial infection in all patients. Patients treated with combination therapy, however, had significantly more watery diarrhea than those treated with erythromycin alone (20 of 37 vs. 10 of 38; $p = .01$). Ten patients developed diarrhea during the last 2 days of the 7-day trial period, but the study drugs were continued until day 7. In all patients, the diarrhea resolved spontaneously after 3.2 ± 1.0 days of withdrawal of prokinetic therapy, and no pharmacologic intervention was required.

DISCUSSION

The current study is the first prospective, double-blind, randomized controlled trial to examine the impact of combination therapy with erythromycin and metoclopramide as the first-line treatment on the outcomes of critically ill patients who did not tolerate enteral feeding. The major findings were that, compared with erythromycin alone, combination therapy was 1) significantly more effective in improving the success of feeding with a lesser degree of tachyphylaxis; 2) associated with the delivery of a significantly greater proportion of prescribed feed to the patients during treatment; 3) associated with a reduced need for postpyloric feeding; and 4) not associated with major adverse effects. Together, these findings suggest that combination therapy is more effective in improving the outcomes of

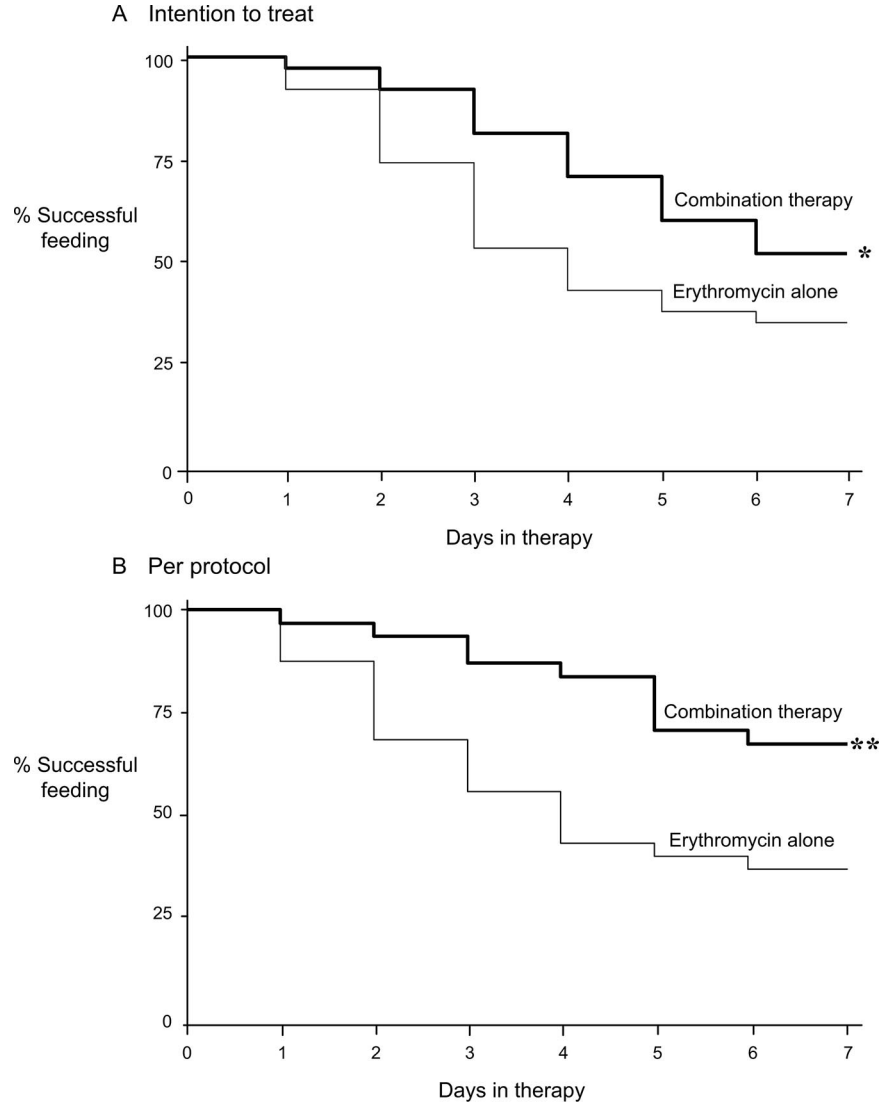

Figure 2. Kaplan-Meier plots depicting the effectiveness of combination and erythromycin-alone therapy on the success of feeding over the 7 days, based on intention to treat (*A*, including all enrolled patients, n = 75) and per-protocol (*B*, including only patients who completed all 7 days of the study, n = 61) analyses. *$p = .04$ vs. erythromycin; **$p < .01$ vs. erythromycin.

enteral feeding than erythromycin alone and should be considered as the first-line therapy for feed intolerance in critical illness.

The presence of intolerance to gastric feeding, by monitoring the GRV, is well recognized as an indirect marker of slow gastric emptying in critically ill patients at risk of aspiration (4, 5, 14, 16, 18, 19–21) and is widely used as a means of monitoring and determining the rate of gastric feeding (3–5). Recent data, however, suggest that the relationship is far from perfect and may lead to unnecessary cessation of feeds and inappropriate starvation in these patients (24). The definition of *feed intolerance* is, at least in part, responsible for this as it encompasses a wide range of aspirate volumes, from 75 to 500 mL (5, 14, 16, 18, 19–21). The Consensus Statement from the North American Summit on aspiration has recommended a high-threshold GRV (500 mL) as a marker to stop enteral feeding (25). Our unit uses a 250 mL-threshold for the GRV as an indication for therapy rather than cessation of enteral feeds. This volume has been used previously by several studies that have examined the effectiveness of various therapies in the treatment of feed intolerance in critically ill patients (5, 16, 20, 21). Furthermore, the positive correlation between the reduced GRV (i.e., improved feed tolerance) with increased caloric intake and reduced need for postpyloric feeding supports the use of GRV monitoring in both clinical and research settings.

In healthy humans, gastric emptying is regulated by several mechanisms through feedback from small intestinal nutrient receptors (26), and both erythromycin and metoclopramide have multiple prokinetic effects on gastrointestinal motor function (27–29). In the current study, the mechanisms underlying the greater prokinetic effect achieved by a combination of metoclopramide and erythromycin are unclear but may relate to complex interactions and multiple actions of the two prokinetic agents on various neurohumoral pathways that mediate gastric emptying (30).

Consistent with a previous study from our unit (20), the effectiveness of iv erythromycin monotherapy diminished after only 3 days of treatment, a phenomenon that has not been observed with oral erythromycin (31, 32). The mechanisms underlying this rapid loss of effectiveness are unclear, although down-regulation, desensitization, and endocytosis of neurohumoral receptors have been proposed as important factors (33, 34). The reasons for a lesser degree of tachyphylaxis with combination therapy are also unknown but are likely to be related to the multiple mechanisms underlying delayed gastric emptying and the complementary actions of the two prokinetic agents. The use of combination therapy is well recognized to prevent the development of drug resistance in the treatment of infection and neoplasia, where a combination of drugs with different modes of action is often used (35, 36). In the current study, the combination of metoclopramide and erythromycin was successful in reducing tachyphylaxis, suggesting that a similar method could be beneficial.

Factors associated with a poor response to prokinetic therapy identified in the current study are consistent with previous findings (3, 7, 12, 20). Sedation with opiates or benzodiazepines severely inhibits gastric motility and emptying (3, 7, 12), which is likely to antagonize the beneficial effect of prokinetic therapy. It is plausible that the high pretreatment GRV is a predictor of poor response, as it reflects the severity of motor dysfunction in these patients. The association between hypo-albuminemia and a poor response to prokinetic therapy suggests the importance of illness severity, as reflected by a higher Acute Physiology and Chronic Health Evaluation II Score on univariate analysis, in gastrointestinal dysmotility and feed intolerance (3, 7, 12).

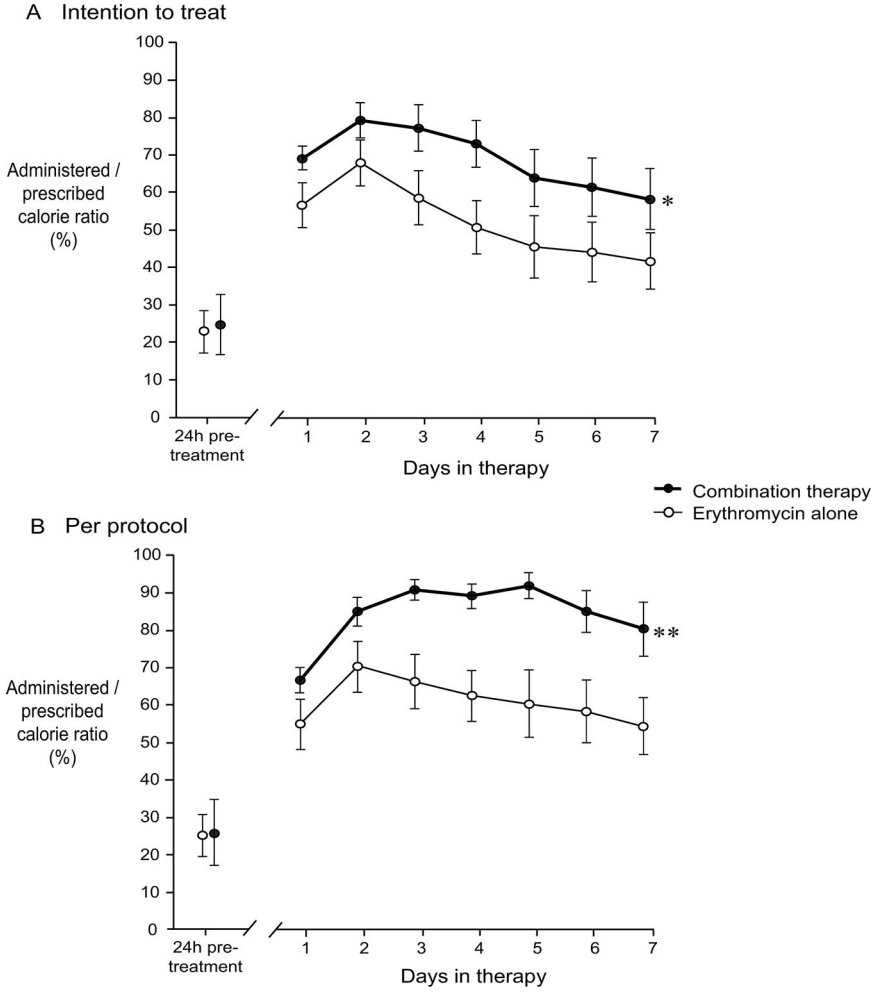

Figure 3. The impact of combination therapy and erythromycin alone on the percentage of administered/prescribed calories over the 7 days, based on intention to treat (*A*, including all enrolled patients, n = 75) and per-protocol (*B*, including only patients who completed all 7 days of the study, n = 61) analyses. *$p = .02$ vs. erythromycin; **$p < .001$ vs. erythromycin.

Table 3. The impact of combination therapy and erythromycin alone on secondary outcomes, based on both intention-to-treat and per-protocol analyses

	Intention-to-Treat Analysis		Per-Protocol Analysis	
	Combination (n = 37)	Erythromycin (n = 38)	Combination (n = 30)	Erythromycin (n = 31)
Postpyloric feeds, n (%)	2 (5)	8 (21)[a]	2 (7)	8 (25)[a]
Vomiting, n (%)	2 (5)	5 (13)	2 (7)	4 (12)
LOS in hospital, days	53.0 ± 6.1	47.8 ± 9.1	57.2 ± 5.7	49.3 ± 8.6
Death in hospital, n (%)	8 (22)	10 (26)	6 (20)	7 (22)

LOS, length of stay.
[a]$p = .04$ vs. combination therapy.

Clinically, the use of erythromycin as a routine prokinetic agent has been applied cautiously, due to potential side effects and the concern of increased bacterial resistance (37, 38). Although the numbers in this study were limited, no major adverse events were seen in either group. Consistent with previous reports (22), watery diarrhea is a relatively common problem in patients receiving enteral feeds and prokinetic drugs. The greater occurrence of diarrhea in the combination-treated group suggests that it has promotility effects on intestinal transit (3, 22, 38). It is important to note that none of the diarrhea in the current study was related to infection, in particular *C. difficile*. Although the widespread use of broad-spectrum antibiotics for the treatment or prophylaxis of infections in the intensive care unit has been documented as a risk factor for the development of antibiotic resistance (3, 22, 23), there are limited data supporting a direct link between antibiotic resistance and a short course of low-dose erythromycin. Even if erythromycin is not used based on this unproven concern, there are no alternative prokinetic agents that are effective and safe. While metoclopramide is significantly less effective than erythromycin (20), cisapride is generally unavailable due to cardiac toxicity (38, 39). Although motilin derivatives have been specifically developed to avoid bacterial resistance, their long-term efficacy has been questioned due to the rapid development of tachyphylaxis (40). Loxiglumide, a cholecystokinin antagonist, has been demonstrated recently to accelerate gastric emptying in healthy humans (41, 42), but its role in the treatment of feed intolerance in critical illness requires further investigation. Given these limitations and the known benefits of enteral nutrition in critically ill patients, short-term use of low-dose erythromycin is a reasonable therapeutic approach for feed intolerance until other effective and safe prokinetic agents become available. Prophylactic use of erythromycin for the prevention of feed intolerance, however, should be avoided.

Although erythromycin has a half-life of only 1.5 hrs, it increases antral motility for >5 hrs (17) and improves the success of feeding for up to 24 hrs in critically ill patients (16). The optimal dosage for iv erythromycin as a prokinetic agent remains unclear and has varied from 200 mg iv twice daily to 250 mg iv four times daily (16–20). In the current study, 200 mg iv twice daily was chosen because positive promotility effects have been demonstrated at this dosage (20) and to minimize the development of drug tachyphylaxis.

Last, in the current study, the benefits of combination therapy on the success of feeding and the amount of nutrients delivered to patients did not translate into improved survival or length of hospital stay. The reason for this is unclear, but it is possible that differences in the secondary outcomes between the two groups were not apparent due to insufficient power of the current study.

CONCLUSION

Combination therapy with erythromycin and metoclopramide is more effective than erythromycin alone in improving the provision of enteral nutrition and should be considered as first-line therapy in the treatment of feed intolerance in critical illness. Tachyphylaxis, however, remains a problem with this regime, and further drug development is required to ensure successful feeding in all patients.

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