

ORIGINAL



Erythromycin versus metoclopramide for post-pyloric spiral nasoenteric tube placement: a randomized non-inferiority trial

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Abstract

Purpose: To determine whether erythromycin is non-inferior to metoclopramide in facilitating post-pyloric placement of self-propelled spiral nasoenteric tubes (NETs) in critically ill patients.

Methods: A prospective, multicenter, open-label, parallel, and non-inferiority randomized controlled trial was conducted comparing erythromycin with metoclopramide in facilitating post-pyloric placement of spiral NETs in critically ill patients admitted to intensive care units (ICUs) of eight tertiary hospitals in China. The primary outcome was procedure success defined as post-pyloric placement (spiral NETs reached the first portion of the duodenum or beyond confirmed by abdominal radiography 24 h after tube insertion).

Results: A total of 5688 patients were admitted to the ICUs. Of these, in 355 patients there was a plan to insert a nasoenteric feeding tube, of whom 332 were randomized, with 167 patients assigned to the erythromycin group and 165 patients assigned to the metoclopramide group. The success rate of post-pyloric placement was 57.5% (96/167) in the erythromycin group, as compared with 50.3% (83/165) in the metoclopramide group (a difference of 7.2%, 95% CI – 3.5% to 17.9%), in the intention-to-treat analysis, not including the prespecified margin of – 10% for non-inferiority. The success rates of post-D1 (reaching the second portion of the duodenum or beyond), post-D2 (reaching the third portion of the duodenum or beyond), post-D3 (reaching the fourth portion of the duodenum or beyond), and proximal jejunum placement and the incidence of any adverse events were not significantly different between the groups.

Conclusions: Erythromycin is non-inferior to metoclopramide in facilitating post-pyloric placement of spiral NETs in critically ill patients. The success rates of post-D1, post-D2, post-D3, and proximal jejunum placement were not significantly different.

Keywords: Self-propelled nasoenteric tubes, Post-pyloric placement, Prokinetic agents, Erythromycin, Metoclopramide, Critically ill patients

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Introduction

Enteral nutrition (EN) via tube feeding is the preferred way of feeding critically ill patients who are unable to have adequate oral intake. Existing guidelines recommend post-pyloric feeding in patients deemed to be at high risk for aspiration or intolerant of intragastric feeding [1–3]. Using a self-propelled spiral nasoenteric tube (NET) for post-pyloric feeding of critically ill patients has emerged as an alternative approach [4–6], especially when endoscopic and fluoroscopic assistance is limited. Spiral NET is designed to utilize peristalsis to pass the tip through the pylorus and on into the duodenum and jejunum [7]. Thus, using prokinetic agents to facilitate transpyloric migration is a sensible strategy, and a randomized controlled trial (RCT) had demonstrated that metoclopramide could improve the success rate of post-pyloric placement of spiral NETs compared with a control group without promotility agents (55.0% vs. 27.3%, $P=0.0001$) [6]. Although several studies of the ability of erythromycin to promote post-pyloric placement of spiral or straight-ended NETs have been reported [8–13], there is limited evidence that erythromycin, as a common prokinetic medication, facilitates transpyloric migration of spiral NETs in critically ill patients.

Therefore, a non-inferiority RCT was designed to assess whether erythromycin is non-inferior to metoclopramide in facilitating post-pyloric placement of spiral NETs in critically ill adults.

Methods

Trial design

This was a prospective, multicenter, open-label, parallel, and non-inferiority RCT performed in the intensive care units (ICUs) of eight tertiary hospitals in China. The study design, which was planned in accordance with the CONSORT statement [14], was approved by the ethic committees of each participating center and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from each patient or their legal surrogates. The trial was registered at <http://www.chictr.org.cn> (registration number ChiCTR-INR-16008211).

Patients

Between October 2016 and July 2018, all patients consecutively admitted to ICUs, at least 18 years old, requiring EN, and with elevated gastric residual (single measurement greater than 150 mL or 12 h cumulative volume greater than 500 mL) [15] were recruited. Exclusion criteria included the presence of an indication for percutaneous gastrostomy or jejunostomy;

Take-home message

Post-pyloric placement of nasoenteric tubes remain a major concern in ICUs, and erythromycin is a promising ancillary drug in this field. This prospective randomized controlled trial of 332 critically ill adults admitted to ICUs demonstrates that erythromycin is non-inferior to metoclopramide in facilitating post-pyloric placement of spiral nasoenteric tubes.

esophageal varices or history of major gastroesophageal surgery (e.g., esophagectomy or gastrectomy); active upper gastrointestinal bleeding; severe nasopharyngeal injuries or stenosis; severe coagulopathy; gastric malignancy, gastrointestinal ulcer, or occlusive ileus; pregnancy; contraindications of erythromycin or metoclopramide; and history of allergy to meglumine diatrizoate.

Eligible patients were randomly assigned to erythromycin or metoclopramide arms at a 1:1 ratio by computer-generated random numbers in blocks of eight to minimize the allocation bias. Each center telephoned the randomization center to verify the groups. None of the investigators was aware of the randomization list prior to group allocation, nor block numbers or block sizes at any moment.

Study intervention

A 145-cm-long, self-propelled spiral NET (CH10, Flo-care Benchmark, Nutricia, Wuxi, China) that was made of radiopaque polyurethane was used in this study. According to the manufacturer's instructions, the feeding tube was inserted in the supine position, with the head tilted at 30°. The tube was straightened using the stylet, and the stylet and tube lumen were lubricated with paraffin. The tube was then inserted 50–55 cm down into the larger nostril. The position was confirmed by air injection into the stomach. The stylet was then pulled out by approximately 25 cm with gentle tugs until loose, and the tube was inserted down 75–80 cm. Before removing the stylet, the position of the tube was again confirmed. Then the stylet was removed and the tube was fixed on the patient's face with a free loop of approximately 40 cm to allow migration.

According to the trial protocol, patients allocated to the metoclopramide group received 20 mg (or 10 mg in cases of renal insufficiency) metoclopramide intravenously 10 min before tube insertion. In the erythromycin group, 500 mg of erythromycin dissolved in 100 mL of 0.9% saline was given intravenously 30 min before insertion and again every 6 h for 24 h once the tube was in the stomach.

Data collection

Once patients were enrolled, data including demographic characteristics, diagnosis, concomitant medication, and severity of illness including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and Acute Gastrointestinal Injury (AGI) grade were collected. The tube tip position confirmed by abdominal radiography 24 h after tube insertion, which was reviewed by an expert group of intensivists and radiologists blinded to this study, was also recorded. If the tube position was difficult to review (e.g., in patients with obesity or gastrointestinal distension), an additional hydrosoluble contrast injection of meglumine diatrizoate was administered via the tube before radiography. The exact location of the tube tips was documented, including the stomach, first (D1), second (D2), third (D3), and fourth (D4) portions of the duodenum, and proximal jejunum. Adverse event data regarding the side effects of study drugs and tube insertion complications were also assessed and recorded. Types of ICU-acquired infections (IAIs, defined as new infections acquired no less than 48 h after ICU admission), infection time points, and isolated microorganisms were documented in the hospital infection monitoring system and transcribed by an expert group of intensivists and infection control staff blinded to this study.

Study outcomes

The primary outcome was procedure success defined as post-pyloric placement (spiral NETs reached the first portion of the duodenum or beyond confirmed by abdominal radiography 24 h after tube insertion). The a priori defined secondary outcome parameters were the success rate of post-D1 (reaching the second portion of the duodenum or beyond), post-D2 (reaching the third portion of the duodenum or beyond), post-D3 (reaching the fourth portion of the duodenum or beyond), and proximal jejunum placement 24 h after tube insertion.

Adverse events

We assessed safety on the basis of the occurrence of study drug side effects, tube insertion complications, and new IAIs (defined as IAIs acquired no less than 48 h after the procedure). Multiple adverse events per patient were analyzed as a single event.

Statistical analysis

On the basis of the findings of previous RCTs, we estimated the procedure success rate to be 61% [12] in the erythromycin group and 55% [6] in the metoclopramide group. Assuming a non-inferiority margin of -10% as clinically acceptable, with a one-sided type I error of 2.5%, a sample size of 149 patients per group calculated

by PASS software (version 13.0) would be required to obtain a statistical power ($1 - \beta$) of 80%. Considering a 10% dropout rate, at least 332 participants were expected to be recruited for the study. To assess for non-inferiority, we used hypothesis testing (one-sided μ test) and derivation of a two-sided 95% confidence interval (CI), where non-inferiority is assumed, if the P value of the test was less than 0.025 and the lower limit of the 95% CI for the difference in procedure success rate exceeded -10% .

The data of categorical variables were reported as number (percentage), as the means \pm standard deviations for continuous variables with normal distribution, and as medians (interquartile ranges) for continuous variables with skewed distribution. The Shapiro–Wilk test was used to detect the normality of data distributions. We used the χ^2 or Fisher exact test for categorical variables and the t test or Mann–Whitney U test for continuous variables according to the distribution to compare the data between two groups. We assessed the study outcomes by intention-to-treat (ITT) analysis and all randomized patients were included in the ITT set. All P values were two-sided except in the test of non-inferiority and were considered statistically significant if the P value was less than 0.05. Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.4 (SAS Inc., Cary, NC, USA).

Results

Enrollment

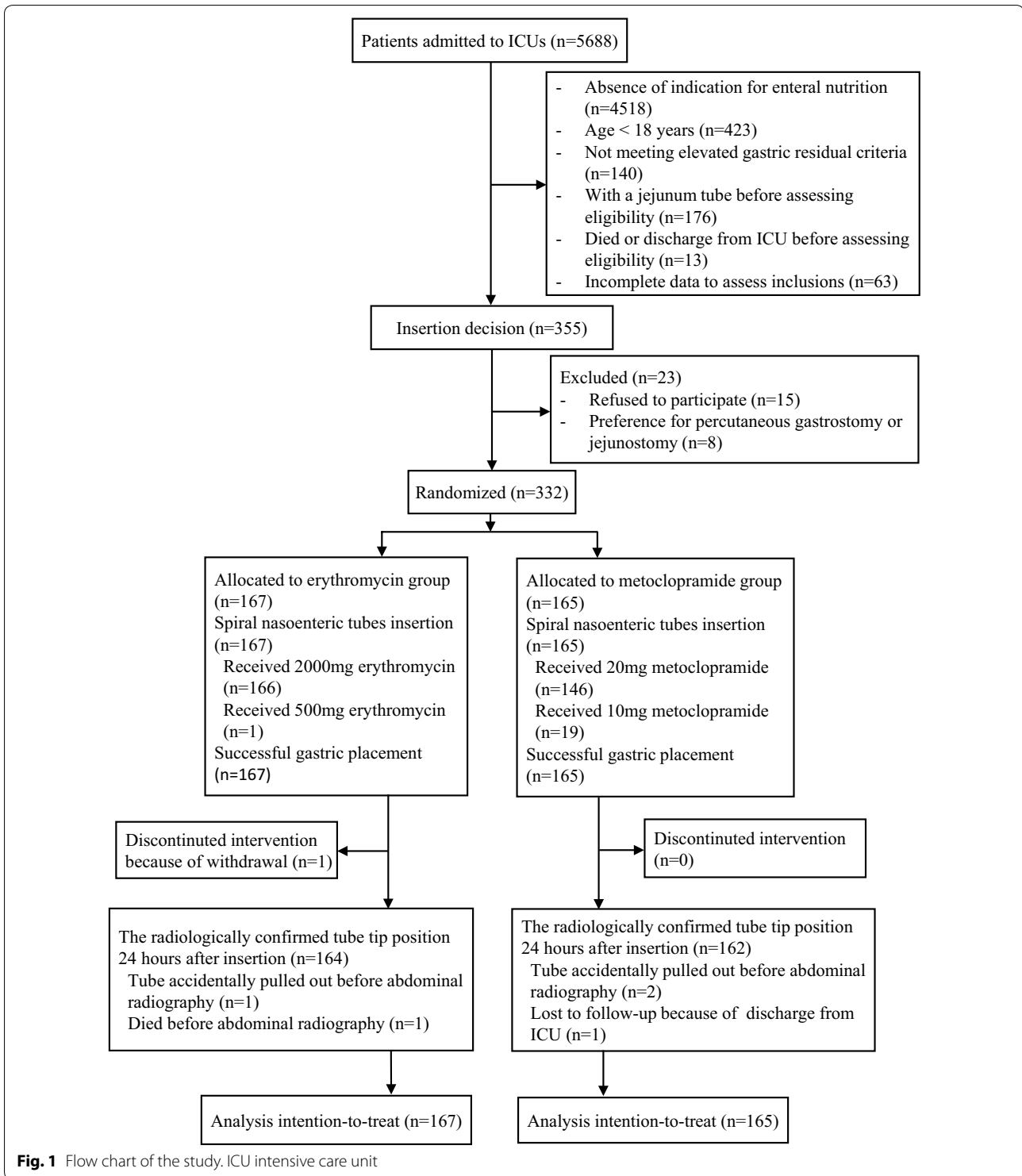
A total of 5688 patients were admitted to ICUs. Of these, in 355 patients there was a plan to insert a nasogastric feeding tube, of whom 332 were randomized, with 167 patients assigned to the erythromycin group and 165 patients assigned to the metoclopramide group (Fig. 1).

Baseline characteristics

The randomized patients' baseline data listed in Table 1 were well balanced between the erythromycin group and metoclopramide group. Most patients admitted to the ICU were diagnosed with nervous system diseases, accounting for 62% of the total. More than half of the patients were treated with mechanical ventilation in both groups. There were no differences in the frequency of use of sedatives, vasopressors, or mechanical ventilation. No significant differences in APACHE II score, SOFA score, or AGI grade were found between the two groups ($P > 0.05$).

Primary outcomes

In the ITT population, there were 96 patients [96/167 (57.5%)] confirmed with successful post-pyloric placement 24 h after insertion in the erythromycin group and 83 patients [83/165 (50.3%)] in the metoclopramide



group, and the procedure success rates were not significantly different between the two groups ($P=0.189$) (Fig. 2). The erythromycin group fulfilled the criteria for non-inferiority to the metoclopramide group in the ITT

analysis. The null hypothesis of inferiority of the erythromycin group to the metoclopramide group was rejected (a difference of 7.2%, 95% CI -3.5% to 17.9%, one-sided $P<0.001$) in the ITT analysis. Moreover, the prespecified

Table 1 Baseline characteristics of trial participants

Variables	Erythromycin group (n = 167)	Metoclopramide group (n = 165)	P value
Age (years)	55.7 ± 17.9	58.7 ± 16.7	0.109
Male	114 (68.3)	115 (69.7)	0.778
Primary diagnosis			
Neurologic	109 (65.3)	97 (58.8)	0.224
Respiratory	18 (10.8)	17 (10.3)	0.888
Gastrointestinal	13 (7.8)	13 (7.9)	0.974
Multitrauma	7 (4.2)	7 (4.2)	0.982
Sepsis	3 (1.8)	6 (3.6)	0.488
Cardiovascular	2 (1.2)	7 (4.2)	0.171
Other	15 (9.0)	18 (10.9)	0.557
Use of sedatives	53 (31.7)	61 (37.0)	0.315
Use of vasopressors	36 (21.6)	31 (18.8)	0.530
Ventilation	105 (62.9)	108 (65.5)	0.624
APACHE II score	21 (16–25)	21 (17–25)	0.592
SOFA score	8 (6–10)	8 (7–10)	0.320
AGI grade			0.475
I	93 (55.7)	83 (50.3)	
II	56 (33.5)	67 (40.6)	
III	18 (10.8)	15 (9.1)	

Data presented as mean ± standard deviation, median (interquartile range), or n (%) unless indicated otherwise

APACHE Acute Physiology and Chronic Health Evaluation, SOFA Sequential Organ Failure Assessment, AGI Acute Gastrointestinal Injury

margin of – 10% was not included in the 95% CI for the difference of the procedure success rate from the metoclopramide group, as shown in Fig. 2. The erythromycin group was not superior to the metoclopramide group because the lower limit of the same CI was less than zero.

Secondary outcomes

In the erythromycin group, tube tips were confirmed to reach D1 in 7 patients (4.2%), D2 in 17 patients (10.2%), D3 in 33 patients (19.8%), D4 in 18 patients (10.8%), and the proximal jejunum in 21 patients (12.6%). Correspondingly, the tube tips were confirmed to reach D1 in 8 patients (4.8%), D2 in 14 patients (8.5%), D3 in 24 patients (14.5%), D4 in 14 patients (8.5%), and the proximal jejunum in 23 patients (13.9%) in the metoclopramide group. The proportion of patients achieving post-D1, post-D2, post-D3, and proximal jejunum was not significantly different between the two groups ($P > 0.05$) (Fig. 2).

Safety

No significant differences were observed in the incidence of any adverse events between the erythromycin group and metoclopramide group according to all documented complications on the agents and tubes within 24 h after tube insertion and new IAI information (OR 1.3; 95% CI 0.8–2.0; $P = 0.313$) (Table 2). In this study, the rate of tube insertion complications was not significantly different between the groups, but the rate of drug side effects in the erythromycin group (11.4%) was higher than that in the metoclopramide group (2.4%) (OR 5.2; 95% CI 1.7–15.5; $P = 0.001$). In addition, diarrhea and liver dysfunction were the most common drug side effects in the erythromycin group, while there were none in the metoclopramide group, and these symptoms were resolved quickly. No tube insertion complications occurred except for nasal mucosa bleeding in 10 patients (3.0%), airway misplacement in 8 patients (2.4%), and bucking in 3 patients (0.9%). Bleeding stopped spontaneously without any treatment, the tube was pulled out immediately

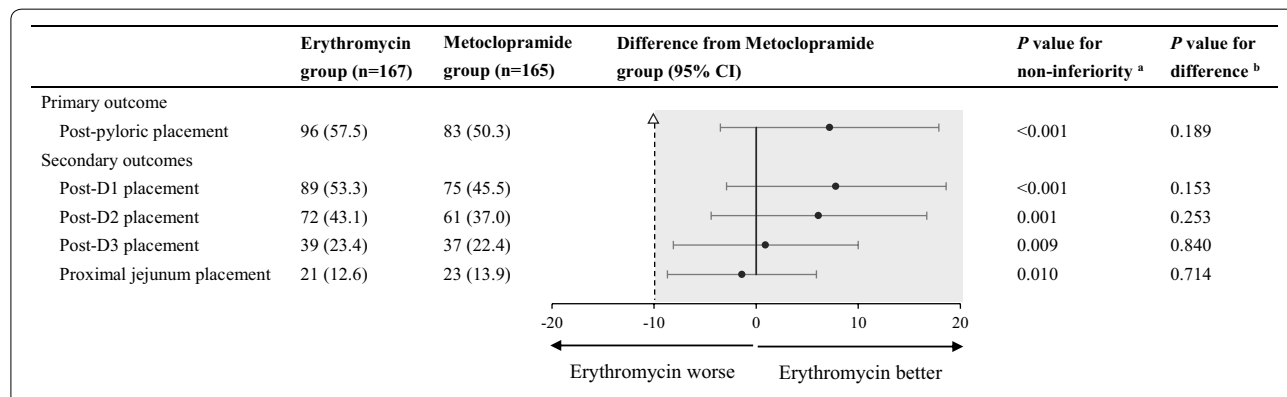


Fig. 2 Primary and secondary outcomes. Data presented as n (%) unless indicated otherwise. Post-pyloric, reaching the first portion of the duodenum or beyond; Post-D1, reaching the second portion of the duodenum or beyond; Post-D2, reaching the third portion of the duodenum or beyond; Post-D3, reaching the fourth portion of the duodenum or beyond. To allow for one-sided testing of non-inferiority, 95% confidence intervals were calculated (shown in black). Confidence intervals within the gray-shaded area are non-inferior. The non-inferiority margin is – 10% (shown as Δ). ^aThe P values were one-sided and were for comparing non-inferiority of erythromycin group with metoclopramide group. ^bThe P values were two-sided and were for comparing the difference of erythromycin group and metoclopramide group

Table 2 Adverse events

Event	Erythromycin group (n = 167)	Metoclopramide group (n = 165)	P value
Any event	54 (32.3)	45 (27.3)	0.313
Drugs side effects	19 (11.4)	4 (2.4)	0.001
Diarrhea	10 (6.0)	0	0.004
Liver dysfunction	9 (5.4)	0	0.007
Nausea	2 (1.2)	2 (1.2)	1.000
Vomiting	2 (1.2)	0	0.499
Debilitation	1 (0.6)	1 (0.6)	1.000
Rash	1 (0.6)	1 (0.6)	1.000
Arrhythmia	1 (0.6)	0	1.000
Jaundice	1 (0.6)	0	1.000
Dizziness	0	1 (0.6)	0.497
Tube insertion complications	10 (6.0)	10 (6.1)	0.978
Airway misplacement	5 (3.0)	3 (1.8)	0.733
Nasal mucosa bleeding	3 (1.8)	7 (4.2)	0.326
Bucking	2 (1.2)	1 (0.6)	1.000
New IAIs	34 (20.4)	35 (21.2)	0.848
New MDR IAIs	12 (7.2)	18 (10.9)	0.237

Data presented as n (%) unless indicated otherwise

IAIs ICU-acquired infections, MDR multidrug-resistant

once airway misplacement or bucking occurred, and no adverse effect occurred. Moreover, new multidrug-resistant (MDR) IAIs occurred in 12 patients (7.2%) in the erythromycin group vs. 18 patients (10.9%) in the metoclopramide group (OR 0.6; 95% CI 0.3–1.4; $P=0.237$) (Table 2).

Discussion

Erythromycin is non-inferior to metoclopramide in facilitating post-pyloric placement of a self-propelled spiral NET in critically ill adults. Furthermore, the success rates of post-D1, post-D2, post-D3, and proximal jejunum placement were not statistically different between the groups.

Erythromycin and metoclopramide, suggested to be initiated in patients with intolerance to enteral feeding or at high risk of aspiration by major guidelines [3, 16], are frequently used as prokinetic agents to promote motility in the ICU. As a specific antagonist of D₂ (dopamine) receptors, metoclopramide was frequently introduced in the procedure of post-pyloric placement in recent studies [17–21]. Given that the effect of metoclopramide has been established in post-pyloric placement of NETs in a previous study, we deemed that patients enrolled should not be left untreated according to ethical principles. Thus, no control group without promotility agents was used. In this trial, patients who received the same dosage

and use of metoclopramide as in our previous trial had a 50.3% procedure success rate.

Erythromycin, a macrolide antibiotic, is another prokinetic agent that has agonistic effects on the motilin receptor located on smooth muscle cells of the antrum and upper duodenum [9, 12], which initiates gastric interdigestive migrating motor complexes (MMCs) that are responsible for the gastric emptying of indigestible particles [22–24]. Previous studies indicated that MMCs presented a dose-dependent response to erythromycin in humans [12, 25], and the dose of erythromycin varied greatly in different post-pyloric placement trials [26, 27]. Thus, 2 g of erythromycin was ultimately chosen on the basis of the dose-dependent property and reference to the drug instruction, although higher doses are available and usually adopted to control *Legionella* infection. The known phenomenon tachyphylaxis is desensitization of the motilin receptor [28, 29], which is rapidly induced after repeated doses and prolonged length of erythromycin and results in a rapid loss of the prokinetic effects [9, 30, 31]. In addition, in our previous study assessing the effect of metoclopramide in post-pyloric placement of spiral NETs, the primary observational time point used was 24 h after tube insertion. Therefore, the initial 24 h after insertion was adopted in the present study. As a result, our post-pyloric tube placement success rate of 57.5% was similar to findings in previous RCTs using a prescribed erythromycin protocol [9, 12], which was non-inferior to metoclopramide.

In terms of safety, serious adverse events were not explicitly reported in various RCTs on erythromycin or metoclopramide [27]. Although serious complications requiring special treatment were absent in our study, 54 patients (32.3%) in the erythromycin group and 45 (27.3%) in the metoclopramide group encountered medication side effects, tube insertion complications, or new IAIs. However, the incidence of diarrhea and liver dysfunction in the erythromycin group was higher than that in the metoclopramide group, which may be attributed to their different pharmacological properties.

Concern about use of erythromycin, a conventional antibiotic, has been expressed because of its role in altering native bacterial flora and increasing the risk of inducing drug-resistant bacteria, particularly *Streptococcus pneumoniae* [32, 33]. Therefore, we strictly followed up members of two groups and faithfully recorded information on new IAIs. Makkar et al. [34] found no significant differences between three groups randomized to receive erythromycin, metoclopramide, or placebo. Similarly, no significant differences in new IAIs were observed between the two study groups. Furthermore, we detected that the new MDR IAI rate did not increase in the erythromycin group compared to that in the metoclopramide

group. It is noteworthy that this study was not designed and might be unable to detect differences based on new IAI results. Thus, this presentation may indicate to some extent that erythromycin used in the short term would not increase the IAI rate.

Although the present trial demonstrated that erythromycin is non-inferior to metoclopramide, it should be noted that indications and contraindications of the two agents may be different. In addition, patients in the erythromycin group were infused with 400 mL more fluid intravenously than were those in the metoclopramide group. Therefore, more attention should be paid to critically ill patients requiring restricted fluid infusion when prescribing erythromycin. We believe that critically ill patients may benefit from a wealth of choices derived from the evidence of this study, especially in highly heterogeneous ICU settings.

To our knowledge, the current study is the largest RCT to date evaluating whether erythromycin is non-inferior to metoclopramide in assisting transpyloric passage of self-propelled spiral NETs in critically ill patients. In the present trial, the failure rates of both groups were approximately 50%, and prokinetic agents showed less-than-satisfactory effects in facilitating post-pyloric placement of spiral NETs. However, a recent study reported that blind bedside post-pyloric placement of a spiral NET following a special procedure, as a rescue therapy subsequent to failed spontaneous post-pyloric migration, achieved an 81.9% post-pyloric placement success rate [5]. Thus, we speculate that the overall expected success rate can be elevated to over 90% when combining both prokinetic agents and rescue therapy [35]. To demonstrate our perspective, a new clinical trial combining both prokinetic agents and rescue therapy has been registered at <http://www.chictr.org.cn> (registration number ChiCTR-INR-16009099). Although alternative bedside methods exist, including endoscopic and electromagnetic guidance post-pyloric placement, and the success rate tends to exceed 90% [36, 37], we believe that this trial enriches the choice for transpyloric placement in a timely manner, especially when resources are limited to access. Given that recent studies have indicated that early EN is associated with improved outcomes [38, 39], our trial may contribute to a better implementation of safe and effective early feeding in patients with critical illness.

Our trial has certain limitations. First, the study was not double-blinded because of the different dosage regimens and the appearance of the two agents. To minimize the potential bias, randomization and adequate allocation concealment were adopted in the trial, and the primary and secondary outcomes were objective rather than subjective. Second, over 60% of the patients in our

trial were primarily diagnosed with neurologic diseases. Therefore, the generalization of our conclusions to all critically ill patients may be limited. Third, the effect of the prokinetic agents when using other self-propelling tubes remains unanswered. Thus, further studies should be performed to enhance the reliability and external validity of the present research conclusions. Finally, some core outcome measures in critical care nutrition research were not measured and reported in the present trial [40].

Conclusions

Our trial indicates that erythromycin is non-inferior to metoclopramide in facilitating post-pyloric placement of spiral NETs in critically ill patients. The success rates of post-D1, post-D2, post-D3, and proximal jejunum placement were not significantly different. Therefore, erythromycin might be effectively and safely used as an alternative to metoclopramide in facilitating post-pyloric placement of spiral NETs in critically ill patients.

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Acknowledgements

The authors would like to thank all the doctors, nurses, technicians, and patients involved in all the participating centers for their dedication in the study.

Author contributions

BH, XOY, and LL equally contributed to the design of the research and interpretation of the data. CC contributed to the conception/design of the research and interpretation of the data and critically revised the manuscript. BH and XOY performed the statistical analysis. All authors contributed to the acquisition and analysis of the data, drafted the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Funding

Bei Hu is currently receiving a Grant (#20181003) from the Administration of Traditional Chinese Medicine of Guangdong Province, China, and a Grant from Guangdong Medical Scientific Research Foundation (#A2018034).

Compliance with ethical standards

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee of the Guangdong General Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Received: 16 August 2018 Accepted: 13 November 2018

Published online: 21 November 2018

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