Original Article

Metoclopramide for preventing nosocomial pneumonia in patients fed via nasogastric tubes: a systematic review and meta-analysis of randomized controlled trials

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Background and Objectives: Metoclopramide, a prokinetic agent, has been recommended to reduce incidence of pneumonia, but its efficacy is controversial. Thus, this systematic review aimed to evaluate the effectiveness of metoclopramide for pneumonia in patients fed via nasogastric tube. **Methods and Study Design:** Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and OVID were searched from their inception to March 31th 2015. Randomized controlled trials (RCTs) of metoclopramide against placebo in patients fed via nasogastric tube were identified. The Cochrane risk of bias assessment tool was used for quality assessment. **Results:** Four trials involving 694 patients fed via nasogastric tube were identified. Compared with placebo, metoclopramide showed no significant effects in reducing pneumonia (n=694; risk ratio [RR]: 0.79; 95% CI: 0.45 to 1.38, p=0.40) or mortality (n=694; RR: 0.93; 95% CI: 0.78 to 1.11, p=0.44). In two trials using continuous data, metoclopramide significantly delayed the development of nosocomial pneumonia (n=80; weighted mean difference [WMD]: 1.74 days; 95% CI: 1.03 to 2.46 days, p<0.00001). However, in two other trials using dichotomous data, metoclopramide increased the proportion of cases showing early-onset nosocomial pneumonia (n=103; RR: 1.32; 95% CI: 1.10 to 1.58, p=0.003). Adverse effects monitoring was reported in one included trial, No significant adverse reactions were noted in this study. **Conclusions:** Because of the poor methodological quality and high risk of bias in the included studies, this systematic review revealed no definite conclusion about the application of metoclopramide for the reduction of nosocomial pneumonia. Therefore, more high-quality studies with larger sample sizes are required.

Key Words: metoclopramide, prevention, pneumonia, enteral feeding; systematic review, meta-analysis

INTRODUCTION

Enteral nutrition by nasogastric tube (NGT) is a common and efficient method of providing nutritional support to prevent malnutrition in hospitalized patients who have adequate gastrointestinal function but are unable to eat.[1-3] Since the mid-20th century, when enteral feeding by NGT was established, the benefits of NGT have been clearly reported in the literature.[4,5] However, pneumonia rate ranges from 33% to 70% in patients fed via NGT.[6-8] NGT feeding results in increased gastric volume and Gram-negative bacterial overgrowth in the stomach.[9-11] Subsequent refluxes of gastric contents into the esophagus and pharynx may lead to tracheal colonization and pneumonia in some patients.[12,13] The physical presence of the NGT across the lower esophageal sphincter itself probably impairs sphincter function and promotes reflux of gastric contents.[14,15] As pneumonia is one of the most common causes of death in tube-fed patients,[7,8] many studies have been conducted in search of ways to best prevent this complication. These include methods to confirm tube placement,[16] professional oral care,[17,18] continuous pump feeding,[19] and prokinetic agent use.[20,21]

Metoclopramide, a prokinetic agent, acts by blocking dopaminergic D2 receptors in the upper gastrointestinal tract.[22] It increases lower esophageal sphincter pressure, gastric antral contractility, and peristalsis in the stomach and duodenum, leading to accelerated gastric emptying and decreased gastroesophageal reflux.[22] This makes it a promising drug for reducing the risk of pneumonia in

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Manuscript received 10 March 2016. Initial review completed 19 April 2016. Revision accepted 11 May 2016.
doi: 10.6133/apjcn.102016.01

patients fed via NGT.[22] Over the past several decades, accumulating data from case reports, case control studies, and RCTs have reported the effectiveness of metoclopramide on pneumonia in patients fed via NGT. However, all these studies were performed in single centers and reported different results. In addition, no review or meta-analysis has been conducted to summarize these research studies. Therefore, the purpose of this systematic review and meta-analysis, including data from RCTs, was to evaluate the efficacy and safety of metoclopramide for nosocomial pneumonia prevention. It was of particular interest to determine whether metoclopramide reduced the nosocomial pneumonia rate in patients fed via NGT.

MATERIALS AND METHODS

Data sources and searches

To identify relevant RCTs, two reviewers (Yanjin Liu and Sen Yang) systematically searched for relevant publications using the electronic databases PubMed, EMBASE, OVID, and the Cochrane Central Register of Controlled Trials, using the search terms "metoclopramide", "metaclopramide", "Methoxyprocainamide" "metoclopramid", "Meclopran" "prokinetic agents," "reglan," "nasogastric feeding tubes" "nosocomial pneumonia," and "lung inflammations". In this study, we included papers dating from the earliest citation in the databases until March 31th 2015. The references of all selected publications and reviews were manually searched for further relevant articles. We did not limit publication languages and types, and even included conference proceedings and theses as long as they met our inclusion criteria.

Study selection

We included all RCTs designed to evaluate the efficacy and safety of metoclopramide during the nasogastric tube feeding period, compared with placebo or no intervention. We did not set limitations on dosages, formulations, or routes of administration of metoclopramide or the types of conventional therapy used. Patients included in these studies were adults aged 18 years and older fed via NGT, no matter what the underlying diseases or gender. The primary outcomes were nosocomial pneumonia rate and the time of onset of pneumonia. Secondary outcomes included enteral nutrition tolerance, adverse effects, length of hospital stay, and mortality.

Data extraction

Two authors (Yanjin Liu and Aixia Wang) independently reviewed all titles, decided on the inclusion of studies based on selection criteria, and then extracted standardized data from each study. Standardized data included first author's name, year of publication, characteristics of participants, number of participants in control and treatment groups, details of interventions, duration of treatment, definition of pneumonia, pneumonia rate, time of onset of pneumonia, mortality, and adverse effects related to metoclopramide. We resolved differences and avoided conflicts by consulting a third author (Xiaofang Dong). If a study had insufficient data to complete data extraction or if we required data clarification, we contacted the authors of the study. We considered the studies to have sufficient data if at least one of the listed outcomes (either primary or secondary) was reported.

Assessment of risk of bias

Two reviewers (Sen Yang and Min Wang) independently evaluated the risk of bias of each study using the assessment tool from the Cochrane Handbook.[23] Any disagreement was discussed among all authors to achieve a consensus. The criteria consisted of the following seven items: (1) sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessments (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other sources of bias.

Data analysis

For dichotomous data (e.g., incidence of pneumonia, early and late onset of pneumonia, and mortality), RR with corresponding 95% CIs were estimated. For continuous data (e.g., days of pneumonia development), WMD with a corresponding 95% CI was used for outcomes pooled on the same scale.

When the quantity and characteristics of studies suggested that meta-analysis was feasible, heterogeneity was measured using the chi-squared test with significance set at $p<0.1$. I^2 was used to estimate the total variation due to heterogeneity across studies.[24] Values of $I^2 \leq 50\%$ were considered to show acceptable heterogeneity and justified use of a fixed effect model for meta-analysis. Otherwise, with $I^2>50\%$, the between-study heterogeneity was substantial and the random-effect models were suitable. We conducted meta-analyses for all outcomes where possible, although the meta-analyses for many of the outcomes should be interpreted with caution due to the presence of substantial heterogeneity. Analyses were considered significant at $p<0.05$.

To assess whether the treatment effect was modified by clinical and demographic variables, we undertook subgroup analyses as follows: (i) different duration of metoclopramide treatment and (ii) different types of participants (stroke patients and critically ill patients). All analyses were conducted using Review Manager, version 5.3 (The Cochrane Collaboration).

RESULTS

Study identification

Figure 1 shows the process of study selection and identification. A total of 106 potentially relevant articles were initially screened in the four electronic databases based on our literature searching strategy. After removing 14 duplicates, 92 articles were identified for further analysis. Through screening of the titles and abstracts, 72 articles were excluded because they were literature reviews, expert opinions, commentaries, case reports, case series, or animal research. The remaining 20 full-text articles were then assessed for eligibility. Of those, 16 articles were excluded for the following reasons: participants did not meet the inclusion criteria (n=10), duplicated data (n=2), not randomized trials (n=2), and intervention included other medical therapies (n=2). Ultimately, four studies were assessed to be eligible in our review (Figure 1).[25-28]

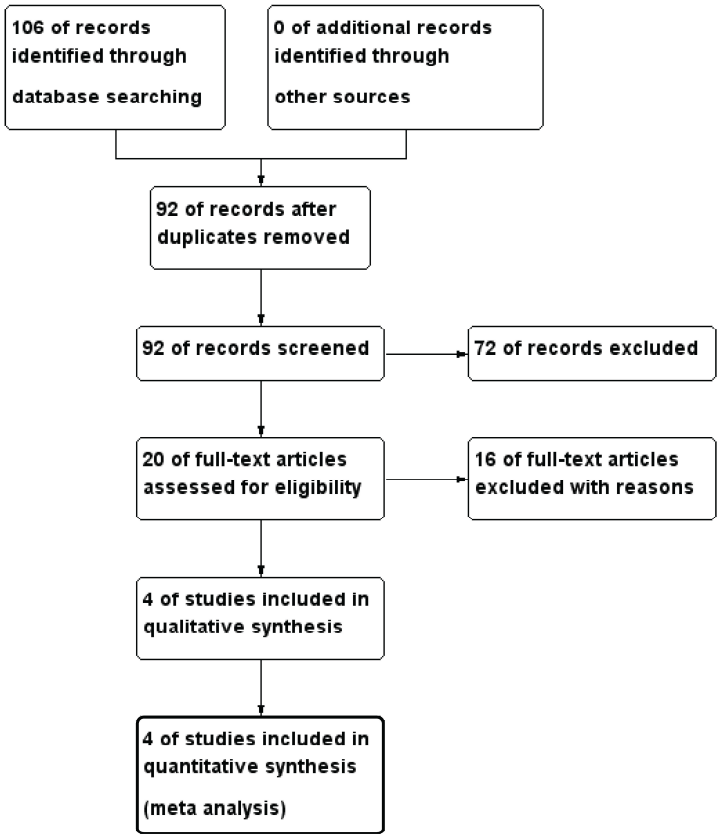

Figure 1. Flow diagram.

Study characteristics

The basic characteristics of the four included randomized trials are summarized in Table 1. A total of 694 patients were enrolled, with 287 in the treatment group and 407 in the control group. The sample size of the studies ranged from 60 to 305 participants. Of these, two compared 5 days of metoclopramide treatment with placebo or no intervention,[26,27] and the other two compared a maximum of 21 days of metoclopramide treatment with placebo.[25,28] We describe the characteristics of the four trials that enrolled stroke patients[25] and critically ill patients.[26-28] The definition of pneumonia varied. The time of onset of pneumonia outcomes was reported in all of the studies: two trials[26,27] used categorical time and two trials[25,28] used continuous days. Mortality was reported in four trials. Adverse effects were reported only in one study.

Risk of bias within studies

In Figure 2, we report the findings obtained with the Cochrane risk of bias tool, whereby trials were judged to show high, unclear, or low risk of bias. The overall risk of bias was low in one trial[25] and high in three trials.[26-28]

Primary outcomes: pneumonia

The meta-analysis showed that metoclopramide treatment was not associated with a significant reduction in the incidence of pneumonia (n=694; RR: 0.79; 95% CI: 0.45 to 1.38, p=0.40; Figure 3), with significant heterogeneity (χ^2=13.2; p=0.004; I^2=77%).

Primary outcomes: time of onset of pneumonia

Four trials evaluated the effect of metoclopramide versus placebo or no intervention on the time of onset of pneumonia. Among these, two trials used continuous days of time and the other two trials used categorical data, comparing late (≥5 days) and early-onset pneumonia (<5 days). In two trials, metoclopramide significantly delayed

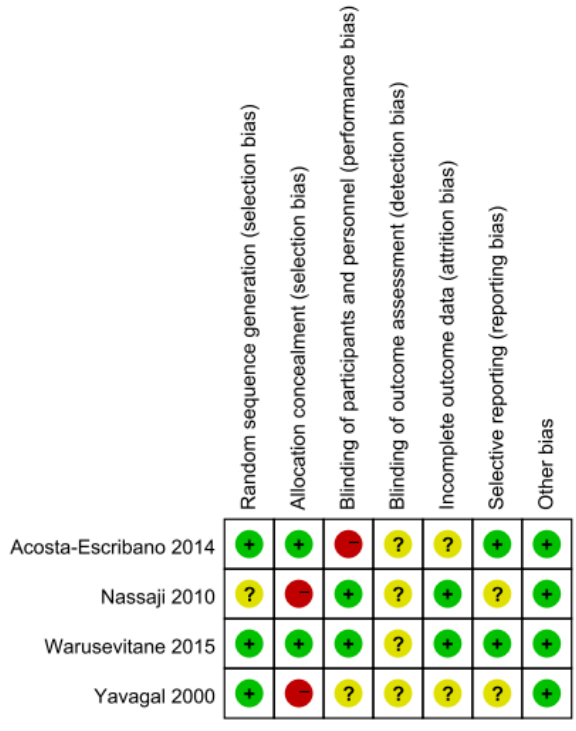

Figure 2. Risk of bias summary.

Table 1. Basic characteristics of the included studies.

Study	Sample size	Setting	Baseline difference	Interventions	Control	Treatment duration	Definition of pneumonia	Outcomes
Nassaji 2010	T:68 C:152	ICU	NSD	10 mg every 8 hrs	No intervention	Maximum of 5 days	Nosocomial pneumonia was diagnosed according to: 1) Axillary temperature; 2) Leukocytosis; 3) Increase in tracheal secretion; 4) New infiltrate on the chest radiograph or progression of an existing infiltrate	a b c
Yavagal 2000	T:131 C:174	ICU	NSD	10 mg every 8 hrs	Placebo	Nasogastric feeding was no longer necessary	Nosocomial pneumonia was diagnosed according to: 1) Appearance of new infiltrates on chest radiograph; 2) A positive tracheal or sputum culture; 3) Fever; d) Leukocytosis	a b c
Warusevitane 2015	T:30 C:30	Stroke unit	NSD	10 mg every 8 hrs	Placebo	Nasogastric feeding was no longer necessary, maximum of 21 days	Pneumonia was diagnosed: 1) At least one other lower respiratory tract symptom; 2) New focal chest signs on examination; 3) At least one systemic feature	a b c d e
Acosta- Escribano 2014	T:58 C:51	ICU	NSD	10 mg every 8 hrs	Placebo	Maximum of 5 days	Ventilator associated pneumonia according to the CPIS criteria	a b c f g

ICU: intensive care unit; T: treatment group; C: control group; NSD: no significant difference.
Outcomes: a) incidence of pneumonia; b) time of onset of pneumonia; c) mortality rate; d) witnessed aspiration; e) adverse events; f) volume of administered diet; g) gastrointestinal complications.

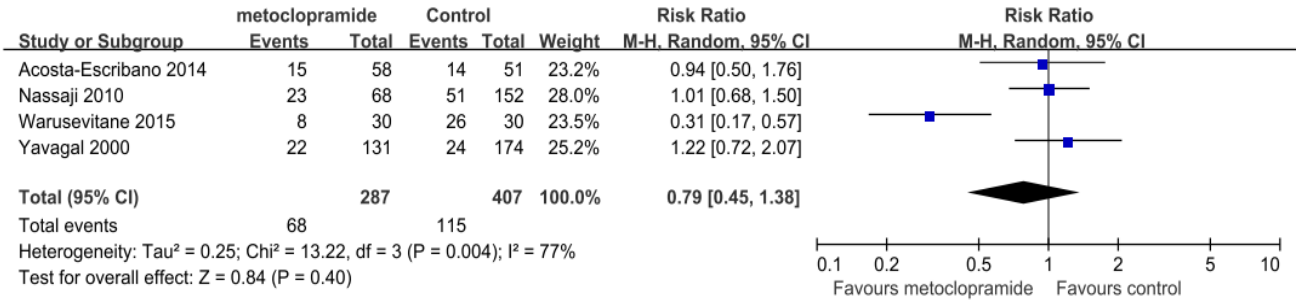

Figure 3. Meta-analysis of metoclopramide use versus placebo or no intervention on nosocomial pneumonia based on the same intervention strategies. CI indicates confidence interval. M-H indicates Mantel-Haenszel.

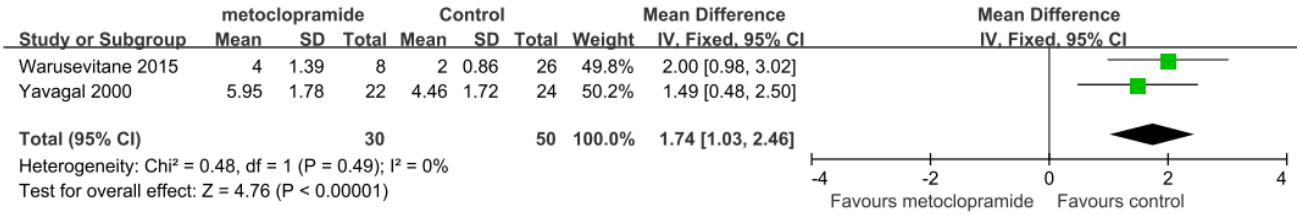

Figure 4. Meta-analysis of metoclopramide use versus placebo or no intervention on pneumonia's time of onset based on the same intervention strategies (continuous data). CI indicates confidence interval. I-V indicates Inverse Variance.

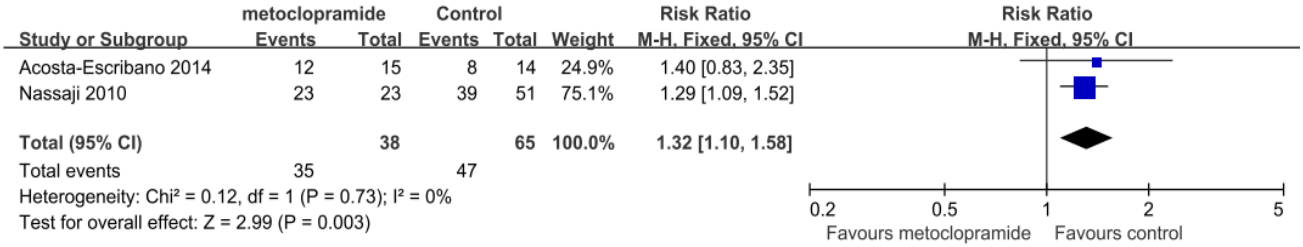

Figure 5. Meta-analysis of metoclopramide use versus placebo or no intervention on pneumonia's time of onset based on the same intervention strategies (dichotomous data). CI indicates confidence interval. M-H indicates Mantel-Haenszel.

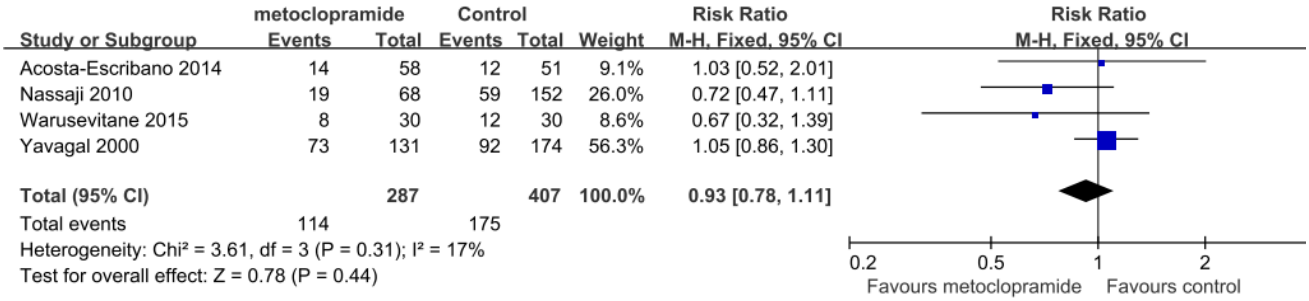

Figure 6. Meta-analysis of metoclopramide use versus placebo or no intervention on mortality based on the same intervention strategies. CI indicates confidence interval. M-H indicates Mantel-Haenszel.

the development of pneumonia (n=80; WMD: 1.74; 95% CI: 1.03 to 2.46, p<0.00001, Figure 4), with no significant heterogeneity (χ^2=0.482; p=0.49; I^2=0%); However, metoclopramide increased the proportion of early-onset pneumonia in another trial (n=103; RR:1.32; 95% CI: 1.10 to 1.58, p=0.003; Figure 5) with no significant heterogeneity (χ^2=0.12; p=0.73; I^2=0%).

Secondary outcomes: mortality

The meta-analysis showed no significant difference between metoclopramide and placebo or no intervention in their effects on mortality reduction (n=694; RR: 0.93; 95% CI: 0.78 to 1.11, p=0.44; Figure 6), with no significant heterogeneity (χ^2=3.61; p=0.31; I^2=17%).

Adverse events

Adverse effects monitoring was reported in one included trial; no significant adverse reactions were noted in this study.

Subgroup analyses

One subgroup analysis, which divided the participants into stroke patients[25] and critically ill patients,[26-28] showed a significant pneumonia reduction associated with the

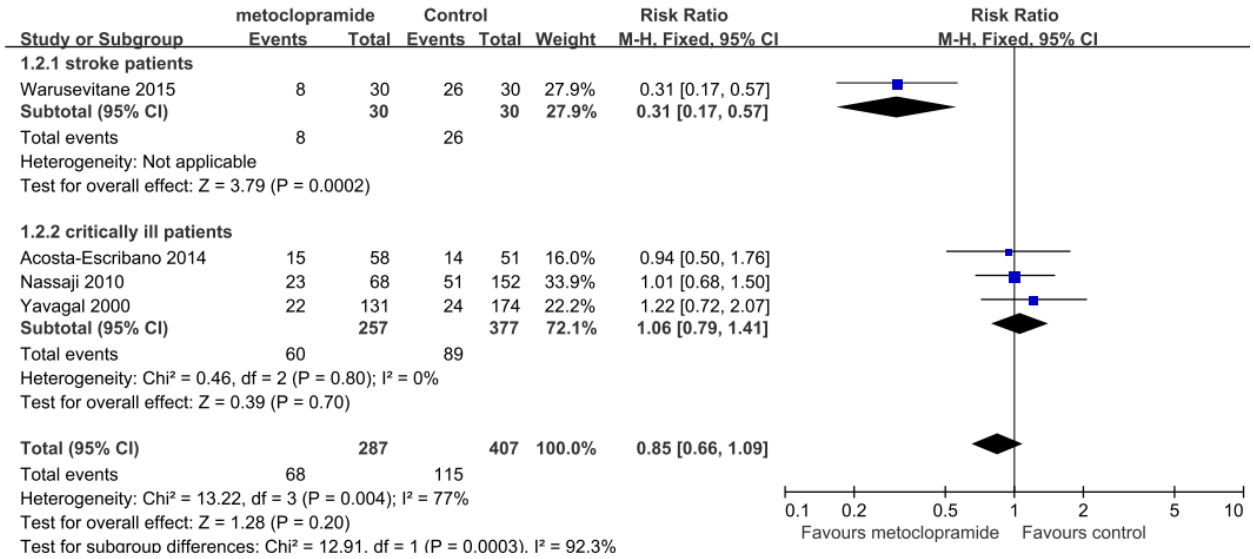

Figure 7. Meta-analysis of different participants' responses to metoclopramide treatment on pneumonia incidence. CI indicates confidence interval. M-H indicates Mantel-Haenszel.

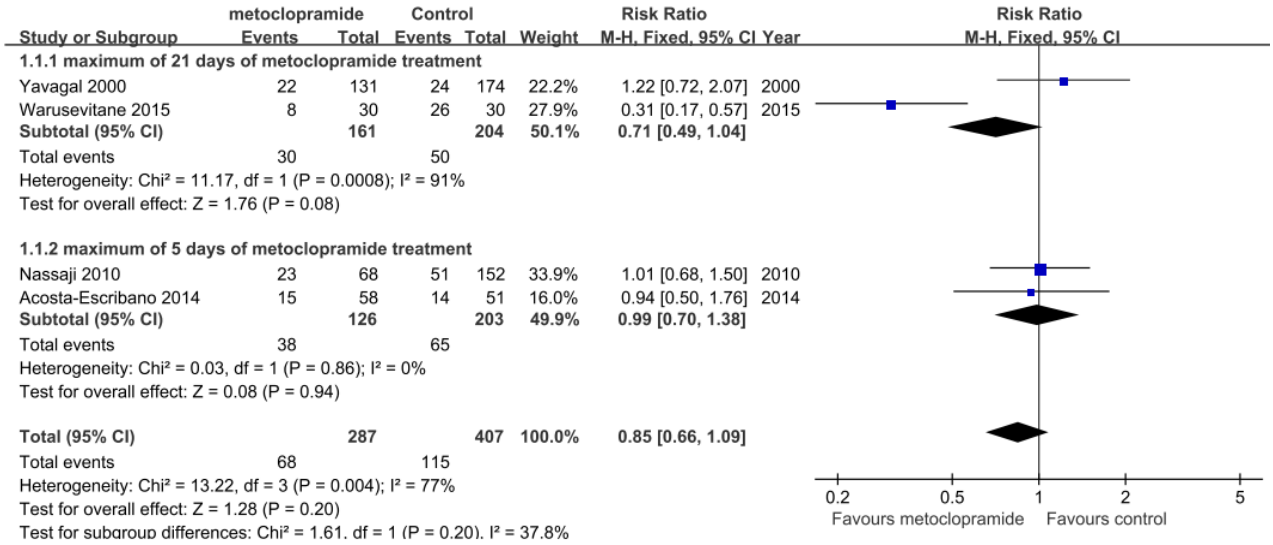

Figure 8. Meta-analysis of different duration of metoclopramide treatment versus placebo or no intervention on pneumonia incidence. CI indicates confidence interval. M-H indicates Mantel-Haenszel.

intervention in stroke patients (Figure 7); however, in critically ill patients, the risk reduction was not significant (Figure 7). Another subgroup analysis showed that neither 21 days nor 5 days of metoclopramide treatment reduced the incidence of pneumonia (Figure 8).

DISCUSSION

Several studies have verified that the presence of a nasogastric tube is associated with increased risk of developing nosocomial pneumonia.[6-8] Enteral feeding further increases the risk of developing pneumonia. Elevation of gastric pH and bacterial contamination of the feeds facilitate gastric colonization by pathogenic Gram-negative bacilli.[9-11]Increased gastric volume and pressure as a result of feeding, a recumbent posture, and impaired gastric emptying promote transfer of the gastric microorganisms into the pharynx and trachea; microaspiration of these secretions into the lower respiratory tract may ultimately produce nosocomial pneumonia. We, therefore, hypothesized that drugs, such as metoclopramide, that can reduce reflux of gastric contents into the esophagus in patients with gastroesophageal reflux disease, may also help reduce the frequency rate of nosocomial pneumonia in patients receiving enteral tube feeds.[28] This systematic review and meta-analysis identified four RCTs investigating the effect of metoclopramide on the incidence of nosocomial pneumonia in patients fed via an NGT. The analysis found that treatment with metoclopramide was neither associated with a significant reduction in the incidence of nosocomial pneumonia nor mortality. Moreover, whether metoclopramide treatment is associated with a lingering development of pneumonia is still worth studying.

The finding that metoclopramide was not associated with a lower incidence of pneumonia is attributable to the dose of metoclopramide (10 mg every 8 hrs) being insufficient to prevent gastroesophageal reflux in critically ill patients.[28] It was reported that comparable doses of meto-

clopramide administered to preoperative patients considerably shortened the gastric emptying time and prevented aspiration of gastric contents during anesthesia and in the postoperative period.[29-31] However, Goldhill et al[32] compared the effect of cisapride with placebo on gastric emptying in critically ill patients fed via enteral nutrition. The results showed that these patients had a large day-to-day variation in gastric motility. Furthermore, despite achieving plasma cisapride levels comparable with those in healthy subjects, the effect of this prokinetic drug on gastric emptying was not consistent. These authors suggest that higher doses of metoclopramide may be required in critically ill patients because many of these patients may have impaired gastroesophageal motility caused by drugs (i.e., opiates, dopamine, and catecholamines), decreased gastric perfusion, or autonomic effects of stress or pain. This was tested in the subgroup analysis in which neither a dose of 10 mg metoclopramide for 21 days nor for 5 days reduced pneumonia rate. However, it is supposed that higher doses of metoclopramide may not be safe in critically ill patients. Doses of 40 mg every day or higher can produce central nervous system toxicity, resulting in drowsiness, restlessness, and extrapyramidal reactions[22], which may occur at lower doses in patients with impaired renal function.

Another explanation for the lack of an effect of metoclopramide on the incidence of nosocomial pneumonia was that the majority of the patients in the four RCTs were critically ill patients. Critically ill patients were much younger (average age 35 years) and majority of these patients were in the postoperative phase with a wide range of complications. Many had further interventions associated with a high risk of reflux and aspiration, such as endotracheal intubation; mechanical ventilation; and treatment with opiates, dopamine, or catecholamine agonists, which could affect peristalsis. For instance, it has been established that the risk of pneumonia associated with enteral feeding is highest in patients receiving mechanical ventilation.[33-35] The main reason is that positive gastric pressure during ventilation may increase the esophageal reflux of gastric contents.[36,37] Moreover, the cuff of the tracheal tube may also compromise the function of the upper esophageal sphincter, increasing microaspiration into the lower respiratory tract.[36] This can also be found in a subgroup analysis of the study in which participants were restricted to stroke patients and all participants were breathing spontaneously. These differences in the patient populations may explain why metoclopramide prevented pneumonia in the stroke patients but not in an intensive care population.

Strengths and limitations

A major strength of this study is the large number of included patients (n=694). In addition, our meta-analysis is the first to include studies assessing the effect of metoclopramide on pneumonia. Moreover, it includes four studies that have not been included in any previous meta-analysis. Previous meta-analyses assessed metoclopramide for post-pyloric placement of feeding tubes.[38] However, some limitations of our study should be acknowledged. Firstly, the distorting effects of publication and location bias on systematic reviews and meta-analyses have been well documented.[39] Secondly, although we are confident that our search strategy located all relevant studies, the most important limitation is the low number of selected study, only four studies were included in this study. Also, the quality scores of the included RCTs were generally poor. Although all of the included studies had a randomization design, only two described the details of the randomization.[25,26] Furthermore, information on allocation concealment or participant and personnel blinding was missing, and only one study reported any details of the blinding of outcome assessments. Although we incorporated all randomized trials relevant to our objective, owing to the small number of included trials, we could not use funnel plot symmetry to assess publication bias. In addition, the categories of pneumonia were variable, including nosocomial pneumonia, pneumonia, and ventilator-associated pneumonia. Inferences about the effect on pneumonia are limited by statistical heterogeneity when four trials are pooled, reflected in an I^2 of 77%. In the trial with a low risk of bias, pneumonia significantly reduced but inferences are limited owing to low event rates and a small sample size.[25] This trial was the only trial that restricted participants to spontaneously breathing stroke patients. It is possible that metoclopramide treatment may reduce incidence of pneumonia in stroke patients. This is supported by the significant subgroup difference between trials that incorporated stroke patients vs. the trial conducted at intensive care units, which partly explains the heterogeneity of the overall pooled findings.

Conclusions

This systematic review and meta-analysis revealed no definite conclusion about the application of metoclopramide for the reduction of pneumonia owing to the poor methodological quality and a high risk of bias. Moreover, no significant impact of this preventive measure was found on the time of onset of pneumonia or mortality. Further studies are required to confirm these results and to evaluate the safety and effectiveness of this preventive measure, especially in stroke patients.

ACKNOWLEDGMENTS

Thanks to Dongyi Zhao for translation of a Spanish article into English. We wish to thank Editage for English language editing.

AUTHOR DISCLOSURES

The authors declare that they have no competing interests.

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