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# Metoclopramide for post-pyloric placement of naso-enteral feeding tubes (Review)

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[Intervention Review]

# Metoclopramide for post-pyloric placement of naso-enteral feeding tubes

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## ABSTRACT

### Background

Enteral nutrition by feeding tube is a common and efficient method of providing nutritional support to prevent malnutrition in hospitalised patients who have adequate gastrointestinal function but who are unable to eat. Gastric feeding may be associated with higher rates of food aspiration and pneumonia than post-pyloric naso-enteral tubes. Thus, enteral feeding tubes are placed directly into the small intestine rather than the stomach, and the use of metoclopramide, a prokinetic agent, has been recommended to achieve post-pyloric placement, but its efficacy is controversial. Moreover, metoclopramide may include adverse reactions, which with high doses or prolonged use may be serious and irreversible.

### Objectives

To determine the effect of intravenous metoclopramide on post-pyloric placement of the naso-enteral tube in adults.

### Search methods

Trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 10) which includes the CUGPD group's specialised register of trials, MEDLINE (1996 to 21 October 2014), EMBASE (1988 to 21 October 2014), LILACS (2005 to 21 October 2014). We did not confine our search to English language publications. Searches in all databases were updated originally in January 2005, then in November 2008 and again in October 2014. No new studies were found in 2008 or in 2014.

### Selection criteria

We selected randomised controlled trials of adults needing enteral nutrition, who received intravenous or intramuscular metoclopramide to aid placement of transpyloric naso-enteral feeding tubes, compared to placebo or no intervention.

### Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. All analyses were performed according to the intention-to-treat method. We present risk ratios (RR) with 95% confidence intervals (CI).

## **Main results**

Four studies, with a total of 204 participants were included and analysed. The trials compared metoclopramide with placebo (two trials) or with no intervention (two trials). Metoclopramide was investigated at doses of 10 mg (two trials) and 20 mg (two trials). There was no statistically significant difference between metoclopramide versus placebo or no intervention administered to promote tube placement (RR 0.82, 95% CI 0.61 to 1.10). Metoclopramide at doses of 10 mg (RR 0.82, 95% CI 0.60 to 1.11) and 20 mg (RR 0.62, 95% CI 0.15 to 2.62) were equally ineffective in facilitating post-pyloric intubation when compared with placebo or no intervention.

## **Authors' conclusions**

In this review, we found only four studies that fitted our inclusion criteria. These were small, underpowered studies, in which metoclopramide was given at doses of 10 mg and 20 mg. Our analysis showed that metoclopramide did not assist post-pyloric placement of naso-enteral feeding tubes.

Ideally randomised clinical trials should be performed that have a significant sample size, administering metoclopramide against control, however, given the lack of efficacy revealed by this review it is unlikely that further studies will be performed.

## **PLAIN LANGUAGE SUMMARY**

### **Metoclopramide for accurate placement of naso-enteral feeding tube**

#### **Background**

When a person is unwell and is unable to eat (or to eat enough), the lack of nutrition can be a serious obstacle to recovery. In these circumstances, feeding through a feeding tube that enters through the nose and passes through the stomach to the small intestine beyond (a post-pyloric naso-enteral feeding tube), is an option.

#### **Review question**

Once the feeding tube has entered the digestive system, placing the feeding tube into the small intestine rather than the stomach is difficult. Metoclopramide (which is also an anti-sickness medication), increases the rate at which the stomach empties, and has tested as a therapy to determine whether it assists with placement of post-pyloric naso-enteral feeding tubes.

Use of metoclopramide is controversial, as it may cause harms (adverse reactions), which may be serious and may include an irreversible neurological condition that can be caused by prolonged use, or high doses of metoclopramide.

#### **Study characteristics**

We originally searched for clinical trials in 2002; and again in 2008 and 2014. We identified four studies that investigated the use of metoclopramide in placement of post-pyloric naso-enteral feeding tubes. The trials included a total of 204 adult participants; 108 participants were treated with metoclopramide, and 96 were given a placebo or no treatment. All four studies were done in hospitals in the USA. The number of participants included in the trials varied from 105 to 10.

The trials were all performed before 1995. They were all small, and examined two different doses of metoclopramide (10 mg and 20 mg), delivered in two different ways (intravenously, and injected into muscle). The way in which they were conducted and reported was poor.

#### **Key results**

Analysis of the four trials revealed that metoclopramide did not have a clear beneficial on the placement of post-pyloric naso-enteral feeding tubes. No harms (adverse reactions) were reported, though it was not clear how thoroughly the people running the trials recorded them. No costs of treatment were reported.

#### **Quality of the evidence**

The quality of the evidence is very low. The four trials were too small to identify any effect clearly; they also used different doses of metoclopramide, (tested against placebo or no treatment). It is unlikely that further studies will be performed to establish whether metoclopramide is helpful in placement of post-pyloric naso-enteral feeding tubes.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Metoclopramide for post-pyloric placement of enteral feeding tubes						
<b>Patient or population:</b> patients needing post-pyloric placement of naso-enteral feeding tubes <b>Settings:</b> hospital <b>Intervention:</b> metoclopramide						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Metoclopramide				
<b>Failure rate of post-pyloric placement of the enteral feeding tube assessed by abdominal radiograph</b> Radiographic assessment of successful tube placement Follow-up: mean 4 hours	<b>Study population</b>		<b>RR 0.82</b> (0.61 to 1.1)	204 (4 studies)	⊕○○○ <b>very low</b> <sup>1,2,3,4</sup>	
	562 per 1000	461 per 1000 (343 to 619)				
	<b>Moderate</b>					
	572 per 1000	469 per 1000 (349 to 629)				

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  
**CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence  
**High quality:** further research is very unlikely to change our confidence in the estimate of effect  
**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate  
**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate  
**Very low quality:** we are very uncertain about the estimate

<sup>1</sup> Design limitation (risk of bias)

<sup>2</sup> Statistical heterogeneity present in the analyses of trials comparing 20 mg metoclopramide versus control

<sup>3</sup> Small number of trials with relatively few participants/events

<sup>4</sup> Insufficient number of studies to assess publication bias using funnel plots

## BACKGROUND

### Description of the condition

Enteral nutrition by feeding tube is a common and efficient method of providing nutritional support to prevent malnutrition in hospitalised patients who have adequate gastrointestinal function but who are unable to eat. Post-pyloric naso-enteral feeding tubes, that enter through the nasal passages and deliver food directly to the duodenum or jejunum, have lower incidence of complications compared to naso-gastric tubes - which deliver food to the stomach - because of their lower rate of gastroesophageal reflux, regurgitation, excessive salivation and irritation of the mucosae. This can be uncomfortable for the patient and also increases the risk of aspiration of food, which can lead to pneumonia. Post-pyloric feeding tube (catheter) placement is not straightforward, but is easier when using manoeuvres such as putting patients in the right-sided lateral position or stimulating them to walk. A stimulating gastric motility drug such as metoclopramide has been used as an auxiliary therapy to promote tube placement. Metoclopramide could also be applied in cases where the tube has successfully entered the digestive system through the throat and into the oesophagus (gullet) and stomach but migration of the tube through the pyloric sphincter (between the stomach and duodenum) is delayed (Troncon 2000).

### Description of the intervention

Metoclopramide is a gastrointestinal stimulant and anti-sickness (antiemetic) drug, which increases the gastric emptiness (Sumner 1986). Metoclopramide has a local stimulating effect on gastric motility and causes the acceleration of gastric emptiness without any concomitant secretion of gastric acid. It is useful for treating gastroesophageal reflux and in disorders of gastric emptiness, but not in the paralytic ileum (Rang 1997).

One study has demonstrated that metoclopramide is useful in post-pyloric feeding tube placement in diabetic patients, increasing the frequency of successful post-pyloric intubation in these patients, but not in non-diabetic patients (Kittinger 1987). In another small study comparing placebo, metoclopramide treatment after tube placement, and metoclopramide treatment before tube placement, duodenal intubation occurred in 90% of patients who received metoclopramide before feeding tube introduction (Kalfarentzos 1987). Metoclopramide is not effective when administered after tube introduction (Whatley 1984). Additionally, metoclopramide may be associated with adverse events, for example, Heiselman 1995 indicated that restlessness, drowsiness, agitation, rashes (urticaria) and occasional drug-induced movement disorders (extrapyramidal reactions) may occur when using metoclopramide at a dose of 20 mg.

### Why it is important to do this review

As there is no systematic review evaluating the effectiveness of parenteral metoclopramide, we will try to answer the following question: is metoclopramide effective and safe for the post-pyloric placement of naso-enteral feeding tubes?

## OBJECTIVES

To determine the effect of intravenous metoclopramide on post-pyloric placement of the naso-enteral tube in adults.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) comparing metoclopramide with placebo or no intervention for the placement of naso-enteral tubes. RCTs were included irrespective of publication status, language or blinding.

#### Types of participants

Participants were all adults (over 18 years of age) receiving parenteral metoclopramide for introduction of enteral feeding tube.

#### Types of interventions

Metoclopramide against placebo or no intervention.

#### Types of outcome measures

##### Primary outcomes

- Success rate of post-pyloric placement of the naso-enteral feeding tube.

##### Secondary outcomes

Adverse reactions including:

- depression;
- high blood pressure;
- decrease of libido;
- headache;
- skin rash;
- fatigue;
- fever;



- hyperactivity;
- insomnia;
- nausea;
- sedation;
- tremor and agitation in the hand;
- dyslalia (speech difficulties);
- dysphagia (swallowing problems).

## Search methods for identification of studies

### Electronic searches

Trials were identified by searching:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 10; [Appendix 1](#)), which includes the CUGPD group's specialised register of trials;
- MEDLINE (1996 to 21 October 2014; [Appendix 2](#));
- EMBASE (1988 to 21 October 2014; [Appendix 3](#));
- LILACS (2005 to 21 October 2014; [Appendix 4](#)).

We did not confine our search to English language publications. Searches in all databases were updated in January 2005 and updated again in November 2008 and October 2014. No new studies were found by the searches in 2008, or in October 2014.

### Searching other resources

We handsearched reference lists from trials selected by electronic searches to identify further relevant trials.

In addition, we contacted members of the Cochrane Upper Gastrointestinal and Pancreatic Diseases (UGPD) review Group, experts in the field, editors of relevant journals and pharmaceutical companies involved in the production of metoclopramide to ask them to supply details of any outstanding clinical trials and relevant unpublished materials.

## Data collection and analysis

### Selection of studies

Two reviewers (CCRS and HS) applied the inclusion criteria to all potential randomised studies. For this updated review CB and CCRS reviewed the results of the updated searches and applied the inclusion criteria to all potential randomised studies. Review authors were not blinded to the reporting of authors' names, journals, date of publication, sources of financial support or results.

### Data extraction and management

Two reviewers (CCRS, HS with CB) independently extracted the following pre-specified characteristics of all included RCTs. In case of discrepancy, the opinion of a fourth reviewer was sought in order to reach a consensus. We extracted data on the: methods, including diagnostic procedure, baseline evaluation of the adequate primary outcomes, and reliability of the outcome measures, complete follow-up; the participants, including age, indication for naso-enteral intubation, number of randomised patients; the intervention dosage, co-intervention in the control group, and route and timing of administration; and outcomes, that is success rate of post-pyloric placement into the duodenum and adverse reactions.

### Assessment of risk of bias in included studies

In this updated review, we independently assessed the risk of bias of the included studies using the risk of bias assessment tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We compared the evaluations, and discussed and resolved any inconsistencies between the review authors' decisions.

We rated the following domains separately for each of the included studies as 'low risk of bias', 'high risk of bias', and 'unclear' when the risk of bias was uncertain or unknown:

- generation of allocation sequence ('sequence generation');
- concealment of allocation ('allocation concealment');
- prevention of knowledge of the allocated interventions during the study ('blinding');
- methods used to address incomplete outcome data;
- selective outcome reporting;
- other sources of bias that could put a study at high risk of bias, including whether a calculation of sample size was carried out.

These assessments are reported in the 'Risk of bias' table for each individual study in the '[Characteristics of included studies](#)' section of the review, and in the '[Risk of bias in included studies](#)' section of this review.

### Measures of treatment effect

We presented dichotomous outcomes data as risk ratios (RR) with their associated 95% confidence intervals; these were analysed in Review Manager 5.3 using the Mantel-Haenszel test and a random-effects model ([RevMan 2014](#)), unless stated otherwise.

### Unit of analysis issues

We did not expect any cross-over trials, as it is unlikely that the participants would be crossed-over to receive an alternative intervention.

If we encountered a multi-armed study, we planned to use data only from the metoclopramide arm versus placebo.

### Dealing with missing data

We attempted to contact investigators to retrieve missing data. We analysed all data by the intention-to-treat method.

### Assessment of heterogeneity

We assessed clinical heterogeneity by examining the trial conditions, that is, the characteristics of the studies, the similarity between the types of participants, and the interventions. Statistical heterogeneity was assessed both by calculation of standard  $\text{Chi}^2$  test and defined as significant when the P value was less than 0.1. When we found heterogeneity we explored the potential causes.

### Assessment of reporting biases

We planned to carry out assessments of reporting bias when at least ten studies were included in a meta-analysis, following the recommendations on testing for funnel plot asymmetry as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to explore possible sources of asymmetry with an additional sensitivity analysis, but in this review we did not have enough included studies to make such analyses feasible.

### Data synthesis

All analyses were performed according to the intention-to-treat method.

We used Review Manager (RevMan 2014), which is the software package provided by Cochrane Collaboration. For dichotomous variables, risk ratio was calculated by random-effects model (DerSimonian 1986). If the overall results had been statistically significant, we planned to calculate the relative risk reduction (RRR),

the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH).

### Subgroup analysis and investigation of heterogeneity

We explored statistical heterogeneity differences in reported effects, methodological heterogeneity, differences in study design and clinical heterogeneity differences between studies in participants characteristics, interventions or outcome measures (Higgins 2011).

We made a post hoc decision to conduct subgroup analyses on the basis of metoclopramide dosage.

### Sensitivity analysis

There were too few included studies in this review to permit sensitivity analysis.

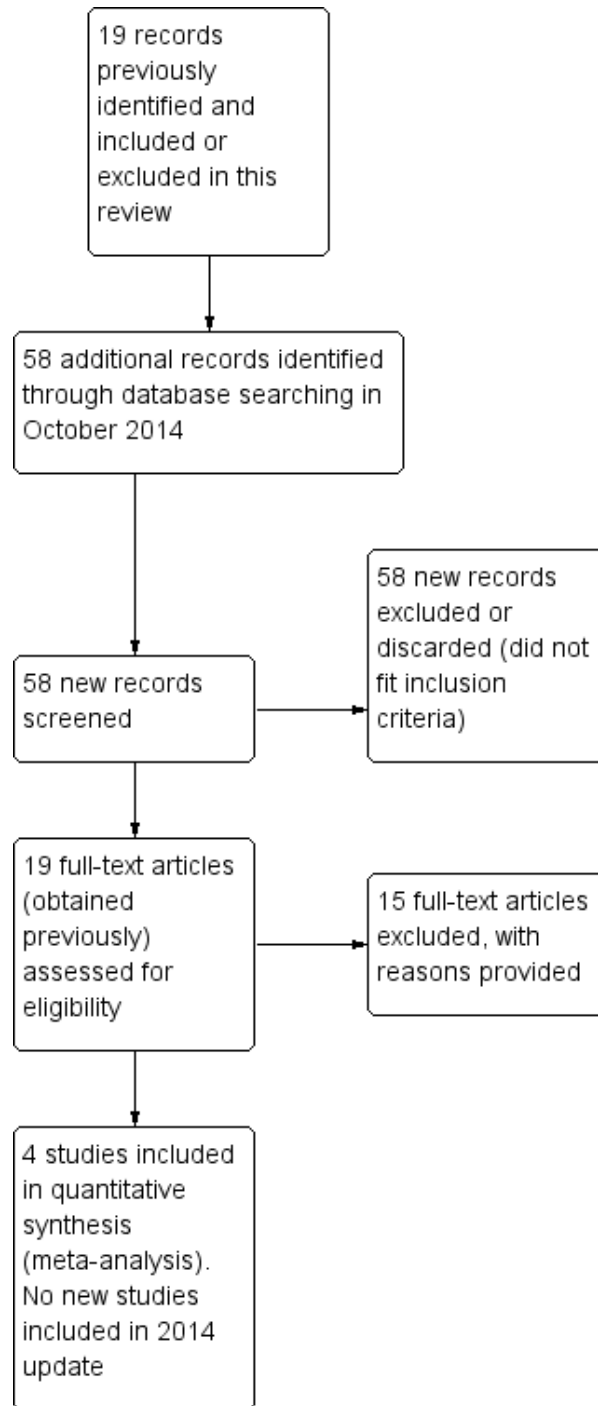
## RESULTS

### Description of studies

#### Results of the search

Nineteen potential studies were identified by electronic and manual searches up to October 2014. A further 58 potential studies were identified from electronic searches in 2014, but no new trials were identified for inclusion at this update (Figure 1).

**Figure 1. Study flow diagram.**



### Included studies

We found four RCTs enrolling a total of 204 participants (Heiselman 1995; Kittinger 1987; Seifert 1987; Whatley 1984; Characteristics of included studies). Of the 204 participants, 108 were treated with metoclopramide, and 96 received placebo or no treatment. Participants designated to undergo treatment with metoclopramide were compared with those allocated to receive placebo or no treatment.

### Participants

The studies included only adult participants. All four included studies were carried out in a secondary care environment, and all were conducted in the USA. Sample sizes varied from 105 in Heiselman 1995, to 70 in Kittinger 1987, 19 in Seifert 1987, and 10 in Whatley 1984.

The Heiselman 1995 study included patients in the critical care unit who required enteral nutrition. In Kittinger 1987 all the participants required feeding tube placement, but pregnant in-patients and intensive care patients were excluded. In Seifert 1987 all patients requiring additional nutrition were eligible for the trial, except for pregnant in-patients and patients currently receiving metoclopramide or neuroleptic patients. The Whatley 1984 study included patients that had previously had failed duodenal intubation. We also collected data on whether diabetic patients were included; Kittinger 1987 included diabetic patients, but this information was not provided in Heiselman 1995, Seifert 1987 or Whatley 1984.

### Intervention

Metoclopramide was given intravenously in three studies (Heiselman 1995; Seifert 1987; Whatley 1984). In one study

metoclopramide was given intramuscularly (Kittinger 1987). Two studies compared metoclopramide with placebo (Kittinger 1987; Seifert 1987), while in the other two studies the control group did not receive any intervention (Heiselman 1995; Whatley 1984).

### Comparison

Metoclopramide versus placebo (Kittinger 1987; Seifert 1987), or no intervention (Heiselman 1995; Whatley 1984).

### Outcomes

All studies analysed whether metoclopramide improved the success rate of post-pyloric feeding tube placement. This was identified by auscultation and abdominal radiography in Heiselman 1995, and by abdominal radiography alone in Kittinger 1987, Seifert 1987 and Whatley 1984. Success rate of transport of pyloric tube placement was evaluated 45 minutes after placement in Heiselman 1995; four hours after insertion of the feeding tube in Seifert 1987 and Whatley 1984; and with an additional abdominal radiograph 24 hours later in some patients who received metoclopramide after feeding tube insertion. In Kittinger 1987, the success rate was evaluated by abdominal radiography one hour after insertion of the feeding tube.

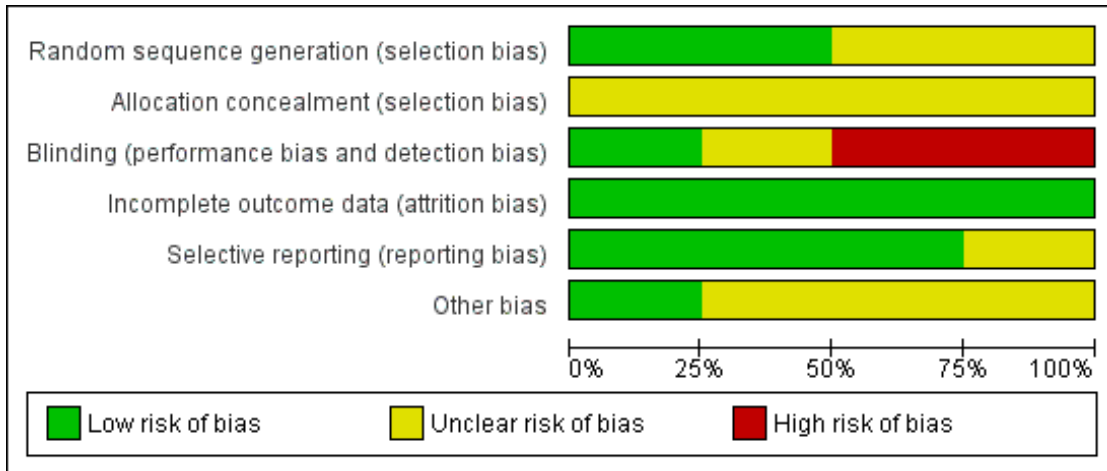
### Excluded studies

Fifteen studies did not fit the inclusion criteria and were not included in this systematic review (see Characteristics of excluded studies).

### Risk of bias in included studies

The risk of bias of included studies is summarised in Figure 2 and Figure 3.

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies**



**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Heiselman 1995	?	?	-	+	?	+
Kittinger 1987	+	?	?	+	+	?
Seifert 1987	?	?	+	+	+	?
Whatley 1984	+	?	-	+	+	?

**Allocation**

Seifert 1987 did not describe the allocation method used, they simply indicated that the studies were randomised.

**Allocation concealment**

There were no descriptions of allocation concealment in the included studies.

**Generation of allocation sequence**

Two studies used a random number table to generate the allocation sequence (Kittinger 1987; Whatley 1984). Heiselman 1995 and

**Blinding**

Two studies were described as double-blind (Seifert 1987; Kittinger 1987), however full details of how this was achieved were not given in the published report of the Kittinger 1987 study. It is therefore unclear whether participants, personnel and outcome assessors were adequately blinded. In Seifert 1987, the participants, nurses investigators and radiologists were blinded to the treatment

protocol. In the remaining two studies there was no description of double-blind methods and we rated these as being at high risk of bias for this domain.

#### Placebo description

Two studies reported a placebo of identical appearance ([Kittinger 1987](#), [Seifert 1987](#)).

#### Incomplete outcome data

Three studies did not have withdrawals or dropouts. One study had withdrawal and reasons of withdrawal were described, but the analysis was not performed on an intention-to-treat basis ([Seifert 1987](#)).

#### Selective reporting

We rated all studies as being at low risk for selective reporting, as outcomes were reported, however we did not have access to the original trial protocols and we were therefore unable to assess whether there were any unpublished outcomes.

#### Other potential sources of bias

##### Sample size calculation

Only one study reported sample size calculation ([Heiselman 1995](#)).

##### Effects of interventions

See: [Summary of findings for the main comparison Metoclopramide for post-pyloric placement of enteral feeding tubes](#)

#### Metoclopramide versus control (placebo or no intervention)

##### Failure rate of post-pyloric placement of enteral feeding tube

In an analysis comparing metoclopramide 10 mg with control ([Heiselman 1995](#); [Kittinger 1987](#)), failure of post-pyloric tube placement of the enteral feeding tube was observed in 41 out of 94 participants (43.7%) using metoclopramide compared with 43 out of 81 (53%) in the control groups. There was no statistically significant difference between the groups (RR 0.82, 95% CI 0.60 to 1.11; 175 participants; 2 studies; [Analysis 1.1](#)). In this comparison there was no statistically significant heterogeneity ( $\text{Chi}^2 = 0.06$ , degrees of freedom (df) = 1, P value 0.81).

In an analysis of studies that used metoclopramide 20 mg versus control ([Seifert 1987](#); [Whatley 1984](#)), failure of post-pyloric tube placement was observed in 7 out of 14 participants in the metoclopramide group (50%) compared with 11 out of 15 in the control group (73%); this difference was not statistically significant (RR 0.62, 95% CI 0.15 to 2.62; 29 participants; 2 studies; [Analysis 1.1](#)). Heterogeneity was observed in this comparison ( $\text{Chi}^2 = 3.48$ , df = 1, P value 0.06).

When we pooled all four trials independent of dosage, the failure rate was 44% (48/108) in the metoclopramide group compared with 56% (54/96) in the control group (RR 0.82, 95% CI 0.61 to 1.10; 204 participants; 4 studies; [Analysis 1.1](#)). In this comparison there was no statistically significant heterogeneity ( $\text{Chi}^2 = 3.24$ , df = 3, P value 0.36).

#### Sensitivity analysis

As there were only four studies with a total of 204 participants, we did not perform sensitivity analysis or investigate publication bias using a funnel plot.

#### Adverse effects

[Seifert 1987](#) reported that no adverse effects attributable to either metoclopramide or placebo were observed. [Kittinger 1987](#) did not report any adverse effects. [Whatley 1984](#) reported that there were no 'side effects' of metoclopramide noted in any participants. [Heiselman 1995](#) noted that adverse effects could include drowsiness, anxiety, agitation and urticaria, and rarely extrapyramidal effects, but did not report adverse effects directly attributable to metoclopramide administered in the course of that study.

## DISCUSSION

#### Summary of main results

[Whatley 1984](#) showed that metoclopramide improves gastric emptying by increasing the amplitude of gastric contractions while relaxing the pyloric sphincter and the duodenal bulb and recorded a significant increase in post-pyloric intubation when metoclopramide was administered prior to the tube insertion. Although that study showed significant results, in our systematic review of four studies, we observed that metoclopramide was not effective in improving the success rate for post-pyloric migration of the enteral tube.

## Overall completeness and applicability of evidence

The four studies included in this systematic review demonstrate that metoclopramide, as administered, did not facilitate post-pyloric intubation in adults. However, the RCTs included had small sample sizes, therefore, we cannot rule out a beneficial effect of metoclopramide. Just one RCT reported that metoclopramide was effective (Whatley 1984). Subgroup analysis in the Kittinger 1987 study, demonstrated that metoclopramide was effective only for people with diabetes mellitus and with evident neuropathy. The other two studies did not find any beneficial effect of metoclopramide (Heiselman 1995; Seifert 1987).

Statistical heterogeneity was found in the comparison of metoclopramide at a dosage of 20 mg. This may be explained by clinical heterogeneity between the studies. The failure rates between the two studies were very different. In the Seifert 1987 study there was a very similar rate between metoclopramide and placebo, whereas in the Whatley 1984 study, the failure rate was lower in the metoclopramide group, at 20%, compared with 100% of those receiving placebo. Other potential sources of heterogeneity were the poor methodological quality of the studies; use of placebo and double-blinding in one study (Seifert 1987); and no intervention and no blinding for the control group in the other study (Whatley 1984).

None of our included studies provided detailed information about adverse effects. Only one study (Heiselman 1995) noted the types of adverse effects that can occur due to metoclopramide but did not report adverse effects directly attributable to metoclopramide administered in the course of that study.

People who are given metoclopramide, especially at doses of 20 mg, may experience adverse reactions which may include depression, high blood pressure, decrease of libido, headache, skin rash, fatigue, fever, hyperactivity, insomnia, nausea, sedation, drowsiness, agitation, and extrapyramidal reactions (impaired speech or impaired swallowing, unsteady gait, inflexibility of upper and lower members, tremor). A recent publication also warns of the risk of developing tardive dyskinesia, or involuntary and repetitive movements of the body, with long-term or high-dose use of metoclopramide (EMA 2013; FDA 2009).

## Quality of the evidence

Potential sources of bias in studies analysing the effect of metoclopramide at the dosage 10 mg for post-pyloric migration of the enteral tube are the timing and methods to evaluate the outcomes; differences in the positioning of patients during the passage of the tube; and ability and experience of the nurse or physician, since training is a factor associated with the successful passage of the naso-enteral tube (Heiselman 1995). Since there were no differences between these studies in relation to timing, administration and dosage of metoclopramide, these explanations do not seem to

justify the heterogeneity observed in these comparisons.

We should, therefore, emphasise that any conclusions we have drawn rely on only four primary studies that had a varying degree of bias due to limitations in trial design. The risk of bias should be considered when interpreting these results (Figure 2), and, given that the findings derive from studies with a high or unclear risk of bias, the findings reported in each study should be viewed with caution.

Overall, the quality of evidence in each comparison was rated as very low and the current body of evidence does not allow robust conclusions to be drawn concerning the efficacy of metoclopramide in assisting post pyloric placement of enteral feeding tubes.

## Potential biases in the review process

We attempted to minimise publication bias by conducting exhaustive searches for trials, however only four studies fitted our inclusion criteria. These were published between 1984 and 1995, with none published since, so we were able to conduct only one meta-analysis. Sensitivity analysis was not possible for primary outcome measures for studies at low risk of bias, as there were too few such studies to permit us to assess the results of the review in this way.

## Agreements and disagreements with other studies or reviews

Whatley 1984 reported that metoclopramide treatment before tube placement was superior to no drug in a small study, however, in the analysis that we carried out using data from four randomised controlled trials including Whatley 1984, in this review, we concluded that metoclopramide was not effective in facilitating post-pyloric placement of naso-enteral feeding tubes.

A network meta-analysis of RCTs of methods to promote placement of post-pyloric feeding tubes, including prokinetic agents (metoclopramide and erythromycin) and gastric air insufflation, was published recently (Huang 2014). The findings of that analysis were broadly in agreement with our study, in that the authors concluded that none of the methods reached statistical significance and that the use of a prokinetic agent might induce more potential adverse reactions. The authors of Huang 2014 recommended that clinicians in clinical practice should no longer use prokinetic agents for this purpose in either paediatric patients or in patients without impaired gastric motility. They also stated that gastric insufflation seems to be clinically better for promoting bedside placement of post-pyloric feeding tubes in adults but in their analysis the results for gastric insufflation did not reach statistical significance compared with other methods, and there are additional safety concerns with this method. It may in fact be that no technique is superior to the standard technique which is bedside placement performed blindly. The authors of Huang 2014 con-



cluded that more large, well-designed RCTs focusing on special populations were required to determine if there are methods that work better than endoscopic placement.

## AUTHORS' CONCLUSIONS

### Implications for practice

We identified no evidence to suggest that metoclopramide enhanced the post-pyloric placement of naso-enteral feeding tubes. None of the studies included in this review specifically addressed adverse effects, and information related to adverse effects can only be derived from reports of studies using metoclopramide for other conditions, which are outside the scope of this review. Adverse events related to long term or high dose use of metoclopramide may include irreversible neurological changes (EMA 2013; FDA 2009)

The Included studies were small and underpowered, used different doses of metoclopramide, and the overall quality of the evidence was very low, with a high risk of bias in several important features of the trials' designs.

### Implications for research

If future research is carried out, it should take the form of well de-

signed and conducted randomised controlled trials (Moher 2001), with a participant population of significant size, administering metoclopramide versus placebo, control or an alternative intervention. Future research would help to evaluate the efficacy of intravenous metoclopramide to facilitate post-pyloric intubation of naso-enteral tubes and establish possible factors of migration (ability and experience of the nurse or physician, decubitus positioning during the passage of the tube, metoclopramide). Participant characteristics should be reported to minimise clinical heterogeneity within the sample. The intervention should compare standard doses of metoclopramide either intravenously or intramuscularly. Post-pyloric intubation should be evaluated by abdominal X-rays within four hours of metoclopramide administration.

The known safety profile of metoclopramide means that recording of adverse events should be a primary outcome of such studies. Given the safety profile and apparent lack of efficacy of this intervention, however, further studies are unlikely to be carried out.

## ACKNOWLEDGEMENTS

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\* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Heiselman 1995

Methods	RCT
Participants	Number of participants randomised: 105; 46 in the control group and 59 in the metoclopramide group Inclusion criteria: admission to the critical care unit; need for enteral nutrition Did not state whether diabetic patients were included or not
Interventions	<ul style="list-style-type: none"> <li>• 59 participants received metoclopramide 10 mg intravenously 10 minutes prior to the insertion of the naso-enteral tube</li> <li>• 46 control participants received no medication prior to the insertion of the naso-enteral tube</li> </ul>
Outcomes	Success rate of post-pyloric tube placement evaluated by auscultation of the right upper abdominal quadrant and abdominal radiography taken 45 minutes after tube advancement
Notes	Setting: Ohio, USA

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details about randomisation provided
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation sequence not described
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, personnel or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals or dropouts
Selective reporting (reporting bias)	Unclear risk	All outcomes reported
Other bias	Low risk	Sample size calculation was reported

**Kittinger 1987**

Methods	RCT
Participants	Number of participants randomised: 70 Inclusion criteria: all patients requiring feeding tube placement were considered eligible, including diabetic patients Exclusion criteria: pregnant in-patients and intensive care patients
Interventions	<ul style="list-style-type: none"> <li>• 35 participants received metoclopramide 10 mg in 2 ml volume intramuscularly</li> <li>• 35 participants received 2 ml of diluent as placebo.</li> </ul> Either metoclopramide or placebo was administered immediately after insertion of the feeding tube
Outcomes	Success rate of post-pyloric tube placement evaluated by abdominal radiography 1 hour after insertion of the feeding tube
Notes	Setting: North Carolina, USA

***Risk of bias***

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Generation of the allocation sequence: random number table
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation sequence not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind method: not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	There are no withdrawals or dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Sample size calculation was not reported

**Seifert 1987**

Methods	RCT
Participants	Number of participants randomised: 19 Inclusion criteria: all patients requiring naso-enteral nutrition were considered eligible Exclusion criteria: pregnant in-patients or patients currently receiving metoclopramide or neuroleptic agents It was not stated whether diabetic patients were included or not

**Seifert 1987** (Continued)

Interventions	<ul style="list-style-type: none"> <li>• 7 participants received metoclopramide 20 mg in 4 ml volume intravenously</li> <li>• 9 participants received 4 ml of normal saline as placebo</li> </ul> <p>Either metoclopramide or placebo were administered 15 minutes prior to the insertion of the naso-enteral tube</p>
Outcomes	Success rate of post-pyloric tube placement evaluated by abdominal radiography 4 hours after insertion of the feeding tube
Notes	Setting: USA

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of the allocation sequence: not described
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation sequence not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind method: the patients, registered nurses, investigators and radiologists were blinded to the treatment protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons were provided for withdrawals and dropouts. 1 participant was lost due to the accidental removal of the tube before the medication was taken and 1 was lost from each group before the X-ray to determine to determine correct placement had taken place
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Intention-to-treat analysis: no Sample size calculation was not reported

**Whatley 1984**

Methods	RCT
Participants	<p>Number of participants randomised:</p> <ul style="list-style-type: none"> <li>• 12 were included in the non-randomised pilot study</li> <li>• a second group of 10 patients (5 in each group) were randomised to receive metoclopramide or placebo</li> </ul> <p>Inclusion criteria: all 22 patients that had failed to achieve spontaneous duodenal intubation were considered eligible</p> <p>Exclusion criteria: no clearly described</p> <p>It was not stated whether diabetic patients were included or not</p>

**Whatley 1984** (Continued)

Interventions	In the randomised comparison: <ul style="list-style-type: none"> <li>• 5 participants received 20 mg of metoclopramide intravenously 10 minutes prior to the reinsertion of weighted tubes</li> <li>• 5 control participants did not receive any intervention</li> </ul>
Outcomes	Success rate of post-pyloric tube placement evaluated by abdominal radiography 4 hours after insertion of the feeding tube. In participants who received metoclopramide after feeding tube insertion, an additional abdominal radiography was also obtained 24 hours later
Notes	Setting: USA

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generation of the allocation sequence: random number table
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation sequence not described
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, personnel or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals or dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Sample size calculation was not reported

**Abbreviation**

RCT: randomised controlled trial

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Beau 1995	Examined the techniques for enteral nutrition, was not an RCT
Gottschlich 1996	Not an RCT
Kalfarentzos 1987	Not an RCT

(Continued)

Kalliafas 1996	Determined whether administration of erythromycin could facilitate passage of a nasogastric feeding tube to the duodenum for post-pyloric feeding
Keshavarzian 1993	Not an RCT, was a crossover study
Kirby 1995	Not an RCT
Levenson 1986	Compared the frequency of duodenal intubations using weighted and un-weighted nasogastric feeding tubes
Levy 1988	Not an RCT
Lord 1992	Compared passage of weighted versus un-weighted enteral feeding tubes
Marian 1993	Not an RCT, was a prospective study.
Schmieding 1997	Not an RCT
Schulz 1993	Not an RCT, was a prospective study
Stern 1994	Determined whether erythromycin ethylsuccinate elixir would facilitate the post-pyloric passage
Thurlow 1985	Not an RCT
Ugo 1992	Not an RCT

**Abbreviation**

RCT: randomised controlled trial



## DATA AND ANALYSES

### Comparison 1. Metoclopramide versus placebo or no intervention for post-pyloric placement of enteral feeding tubes

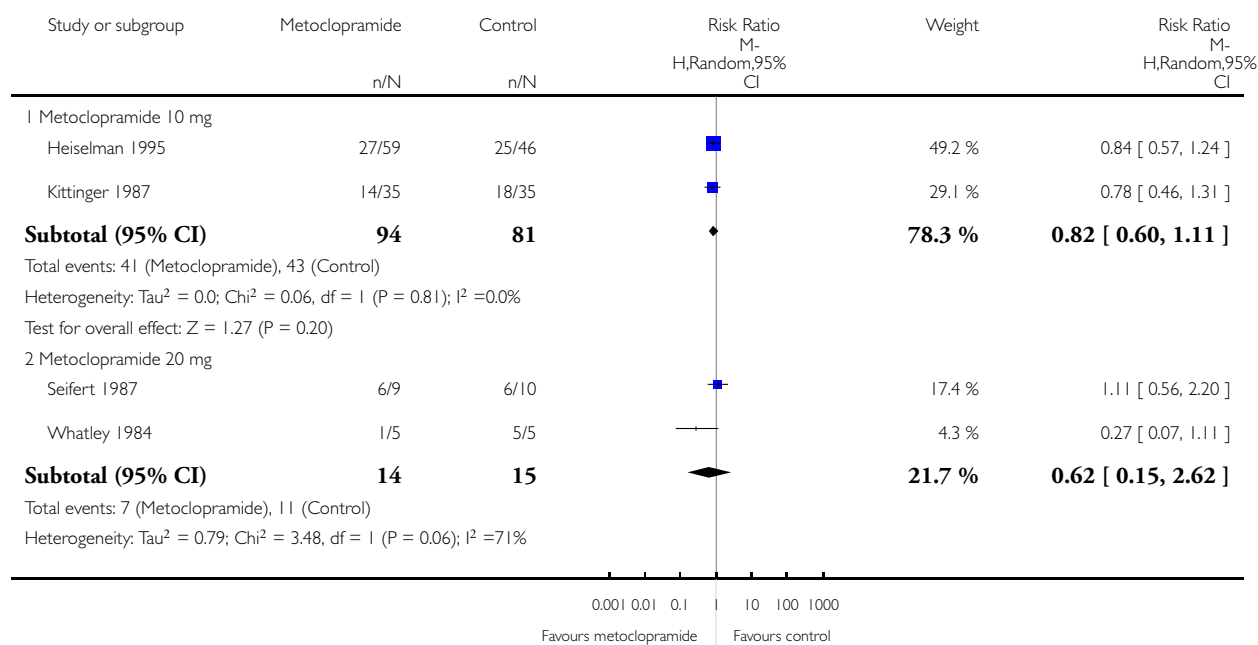
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure rate of transpyloric placement of the enteral feeding tube assessed by abdominal radiograph	4	204	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.61, 1.10]
1.1 Metoclopramide 10 mg	2	175	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.60, 1.11]
1.2 Metoclopramide 20 mg	2	29	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.15, 2.62]

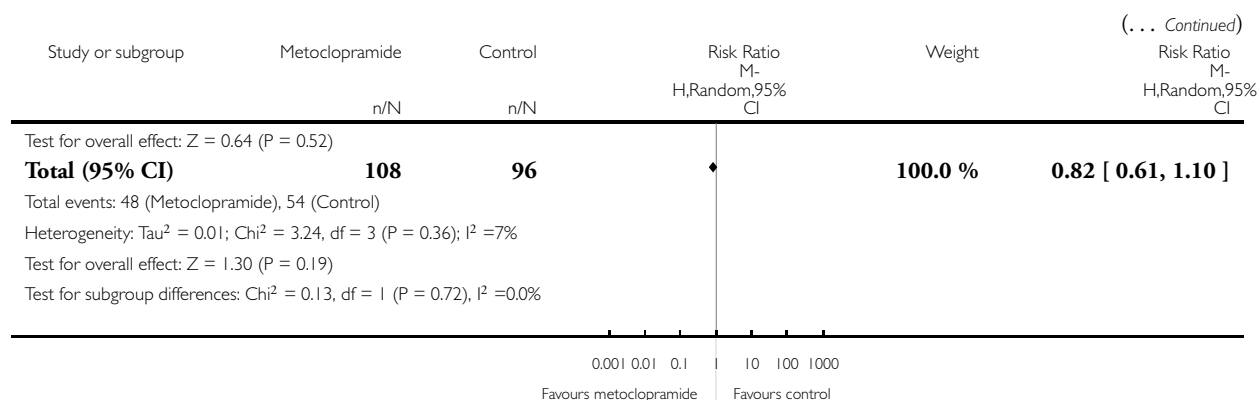
#### Analysis 1.1. Comparison 1 Metoclopramide versus placebo or no intervention for post-pyloric placement of enteral feeding tubes, Outcome 1 Failure rate of transpyloric placement of the enteral feeding tube assessed by abdominal radiograph.

Review: Metoclopramide for post-pyloric placement of naso-enteral feeding tubes

Comparison: 1 Metoclopramide versus placebo or no intervention for post-pyloric placement of enteral feeding tubes

Outcome: 1 Failure rate of transpyloric placement of the enteral feeding tube assessed by abdominal radiograph





## APPENDICES

### Appendix I. CENTRAL search strategy

OVID EBM Reviews - Cochrane Central Register of Controlled Trials <September 2014>

- 1 exp enteral nutrition/ (1307)
- 2 (enter\$ adj3 feed\$).tw. (864)
- 3 (enter\$ adj3 nutrit\$).tw. (1837)
- 4 or/1-3 (2879)
- 5 exp Intubation, Gastrointestinal/ (527)
- 6 (nasenteral\$ or naso enteral\$).tw. (16)
- 7 (esophag\$ adj3 intubat\$).tw. (64)
- 8 (oesophag\$ adj3 intubat\$).tw. (54)
- 9 (duoden\$ adj3 intubat\$).tw. (28)
- 10 (gastrointest\$ adj3 intubat\$).tw. (4)
- 11 (gastric adj3 intubat\$).tw. (70)
- 12 (esophag\$ adj3 catheter\$).tw. (40)
- 13 (oesophag\$ adj3 catheter\$).tw. (18)
- 14 (duoden\$ adj3 catheter\$).tw. (6)
- 15 (stomach adj3 intubat\$).tw. (12)
- 16 (stomach adj3 catheter\$).tw. (7)
- 17 (gastrointest\$ adj3 catheter\$).tw. (3)
- 18 (gastric adj3 catheter\$).tw. (19)
- 19 exp gastrointestinal motility/ (2442)
- 20 exp gastric emptying/ (1141)
- 21 (stomach adj3 emptying).tw. (97)
- 22 (gastric adj3 emptying).tw. (1870)
- 23 (gastro\$ adj3 motili\$).tw. (413)
- 24 (gastric adj3 motili\$).tw. (306)
- 25 or/5-24 (4251)
- 26 exp metoclopramide/ (954)

27 (Metoclopramide or Cerucal or 5 Chloro 2 Methoxyprocainamide or Clodilion or Clopra or Del 1267 or Del1267 or Diber-til or Duraclamid or Emenil or Emetard or Emitasol or Encil or Gastrobid or Gastronerton or Gastrosil or Gastrotem or Gastro Timelets or Gastrotimelets or Hyrin or M 813 or M813 or Maxeran or Maxeron or Maxolan or Maxolon or Meclopramide or Meclo-pramide or Meclopran or Metaclopramide or Methochlopramide or Methoclopramide or Methoclopramine or Metochlopramide or Metoclopramide or Metoclopramid or Metoclopramine or Metoclopranide Hydrochloride or Metaclopramide or Metoclorpramide or Metodopramide or Metopram or Metox or Metpamid or Mygdalon or Neu Sensamide or Octamide or Paspertin or Perinorm or Plasil or Pramidin or Pramin or Primperan or Reclomide or Reglan or Rimetin or Sensamide or Tomid).tw. (1717)

28 or/26-27 (1783)

29 4 and 25 and 28 (22)

## Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1 randomized controlled trial.pt. (397350)

2 controlled clinical trial.pt. (90496)

3 randomized.ab. (316885)

4 placebo.ab. (162975)

5 drug therapy.fs. (1775294)

6 randomly.ab. (227206)

7 trial.ab. (330636)

8 groups.ab. (1429199)

9 or/1-8 (3509100)

10 exp animals/ not humans.sh. (4077582)

11 9 not 10 (3013932)

12 exp enteral nutrition/ (16146)

13 (enter\$ adj3 feed\$).tw. (5972)

14 (enter\$ adj3 nutrit\$).tw. (6942)

15 or/12-14 (20878)

16 exp Intubation, Gastrointestinal/ (8571)

17 (nasoenteral\$ or naso enteral\$).tw. (139)

18 (esophag\$ adj3 intubat\$).tw. (601)

19 (oesophag\$ adj3 intubat\$).tw. (242)

20 (duoden\$ adj3 intubat\$).tw. (382)

21 (gastrointest\$ adj3 intubat\$).tw. (52)

22 (gastric adj3 intubat\$).tw. (984)

23 (esophag\$ adj3 catheter\$).tw. (376)

24 (oesophag\$ adj3 catheter\$).tw. (100)

25 (duoden\$ adj3 catheter\$).tw. (260)

26 (stomach adj3 intubat\$).tw. (120)

27 (stomach adj3 catheter\$).tw. (84)

28 (gastrointest\$ adj3 catheter\$).tw. (43)

29 (gastric adj3 catheter\$).tw. (259)

30 exp gastrointestinal motility/ (33836)

31 exp gastric emptying/ (9078)

32 (stomach adj3 emptying).tw. (442)

33 (gastric adj3 emptying).tw. (10373)

34 (gastro\$ adj3 motili\$).tw. (4222)

35 (gastric adj3 motili\$).tw. (2905)

36 or/16-35 (50241)

37 exp metoclopramide/ (4635)

38 (Metoclopramide or Cerucal or 5 Chloro 2 Methoxyprocainamide or Clodilion or Clopra or Del 1267 or Del1267 or Diber-til or Duraclamid or Emenil or Emetard or Emitasol or Encil or Gastrobid or Gastronerton or Gastrosil or Gastrotem or Gastro

Timelets or Gastrottimelets or Hyrin or M 813 or M813 or Maxeran or Maxeron or Maxolan or Maxolon or Meclopamide or Meclopramide or Meclopran or Metaclopramide or Methochlopramide or Methoclopramide or Methoclopramine or Metochlopramide or Metoclopramide or Metoclopramid or Metoclopramine or Metoclopranide Hydrochloride or Metaclopramide or Metoclorpramide or Metodopramide or Metopram or Metox or Metpamid or Mygdalon or Neu Sensamide or Octamide or Paspertin or Perinorm or Plasil or Pramidin or Pramin or Primperan or Reclomide or Reglan or Rimetin or Sensamide or Tomid).tw. (5631)

39 or/37-38 (6628)

40 15 and 36 and 39 (63)

41 11 and 40 (39)

42 limit 41 to ed=20080101-20141021 (13)

### Appendix 3. EMBASE search strategy

1996 to 2014 Week 42

1 Clinical trial/ (687540)

2 Randomized controlled trial/ (306414)

3 Randomization/ (55320)

4 Single blind procedure/ (17566)

5 Double blind procedure/ (91805)

6 Crossover procedure/ (36116)

7 Placebo/ (200584)

8 Randomized controlled trial\$.tw. (101060)

9 Rct.tw. (14607)

10 Random allocation.tw. (1055)

11 Randomly allocated.tw. (17036)

12 Allocated randomly.tw. (1316)

13 (allocated adj2 random).tw. (286)

14 Single blind\$.tw. (11523)

15 Double blind\$.tw. (102885)

16 ((treble or triple) adj blind\$.tw. (337)

17 Placebo\$.tw. (158223)

18 Prospective study/ (242685)

19 or/1-18 (1162726)

20 Case study/ (25629)

21 Case report.tw. (196639)

22 Abstract report/ or letter/ (563718)

23 or/20-22 (780796)

24 19 not 23 (1132564)

25 exp enteral nutrition/ (15911)

26 (enter\$ adj3 feed\$.tw. (5886)

27 (enter\$ adj3 nutrit\$.tw. (8814)

28 or/25-27 (19640)

29 exp Intubation, Gastrointestinal/ (2924)

30 (nasoenteral\$ or naso enteral\$.tw. (117)

31 (esophag\$ adj3 intubat\$.tw. (449)

32 (oesophag\$ adj3 intubat\$.tw. (158)

33 (duoden\$ adj3 intubat\$.tw. (96)

34 (gastrointest\$ adj3 intubat\$.tw. (21)

35 (gastric adj3 intubat\$.tw. (440)

36 (esophag\$ adj3 catheter\$.tw. (362)

37 (oesophag\$ adj3 catheter\$.tw. (91)

38 (duoden\$ adj3 catheter\$.tw. (134)

39 (stomach adj3 intubat\$.tw. (58)

40 (stomach adj3 catheter\$.tw. (46)  
 41 (gastrointest\$ adj3 catheter\$.tw. (36)  
 42 (gastric adj3 catheter\$.tw. (224)  
 43 exp gastrointestinal motility/ (14371)  
 44 exp gastric emptying/ (10625)  
 45 (stomach adj3 emptying).tw. (230)  
 46 (gastric adj3 emptying).tw. (8625)  
 47 (gastro\$ adj3 motili\$.tw. (3722)  
 48 (gastric adj3 motili\$.tw. (2146)  
 49 or/29-48 (29479)  
 50 exp metoclopramide/ (12043)  
 51 (Metoclopramide or Cerucal or 5 Chloro 2 Methoxyprocaïnamide or Clodilium or Clopra or Del 1267 or Del1267 or Diber-  
 til or Duraclamid or Emenil or Emetard or Emitasol or Encil or Gastrobid or Gastronerton or Gastrosil or Gastrotem or Gastro  
 Timelets or Gastrotimelets or Hyrin or M 813 or M813 or Maxeran or Maxeron or Maxolan or Maxolon or Meclopamide or Meclo-  
 pramide or Meclopran or Metaclopramide or Methochlopramide or Methoclopramide or Methoclopramine or Metochlopramide or  
 Metoclopramide or Metoclopramid or Metoclopramine or Metoclopranide Hydrochloride or Metaclopramide or Metoclorpramide or  
 Metodopramide or Metopram or Metox or Metpamid or Mygdalon or Neu Sensamide or Octamide or Paspertin or Perinorm or Plasil  
 or Pramidin or Pramin or Primperan or Reclomide or Reglan or Rimetin or Sensamide or Tomid).tw. (3489)  
 52 or/50-51 (12282)  
 53 28 and 49 and 52 (154)  
 54 24 and 53 (60)  
 55 limit 54 to em=200801-201442 (22)

#### Appendix 4. LILACS search strategy

(tw:(Metoclopramide or Cerucal or 5 Chloro 2 Methoxyprocaïnamide or Clodilium or Clopra or Del 1267 or Del1267 or Diber-  
 til or Duraclamid or Emenil or Emetard or Emitasol or Encil or Gastrobid or Gastronerton or Gastrosil or Gastrotem or Gastro  
 Timelets or Gastrotimelets or Hyrin or M 813 or M813 or Maxeran or Maxeron or Maxolan or Maxolon or Meclopamide or Meclo-  
 pramide or Meclopran or Metaclopramide or Methochlopramide or Methoclopramide or Methoclopramine or Metochlopramide or  
 Metoclopramide or Metoclopramid or Metoclopramine or Metoclopranide Hydrochloride or Metaclopramide or Metoclorpramide or  
 Metodopramide or Metopram or Metox or Metpamid or Mygdalon or Neu Sensamide or Octamide or Paspertin or Perinorm or Plasil  
 or Pramidin or Pramin or Primperan or Reclomide or Reglan or Rimetin or Sensamide or Tomid)) AND (year'cluster:(2008-2014))

#### WHAT'S NEW

Last assessed as up-to-date: 21 October 2014.

Date	Event	Description
21 October 2014	New citation required but conclusions have not changed	Literature search was re-run, with 58 new studies identified, no new studies fitted the inclusion criteria
21 October 2014	New search has been performed	Updated format of review to current standards, conclusions unchanged New author (CB) added.

## HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 4, 2002

Date	Event	Description
10 December 2008	New search has been performed	Updated
30 October 2008	New search has been performed	Converted to new review format.
14 October 2005	Amended	New studies sought but none found
23 August 2004	New search has been performed	Minor update
5 August 2002	New citation required and conclusions have changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

All authors, Cristiane Costa Reis da Silva, Humberto Saconato, Álvaro N Atallah, contributed equally to the production of the review including data extraction, data synthesis and writing the text. Cathy Bennett assisted with all aspects of review writing for the update produced in 2014.

## DECLARATIONS OF INTEREST

Cathy Bennett is the proprietor of Systematic Research Ltd. and received a consultancy fee for her work on this review, she is also an editor of the Cochrane UGPD group. To prevent conflict of interest, the updated review was assessed independently by Prof Paul Moayyedi and Dr Grigoris Leontiades (CUGPD co-ordinating editors) prior to publication.

Cristiane Costa Reis da Silva: nothing to declare.

Humberto Saconato: nothing to declare.

Álvaro N Atallah: nothing to declare.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this updated review, we no longer use the Jadad scale to assess methodological quality (Jadad 1996). Instead we independently assessed the risk of bias in the included studies using the risk of bias assessment tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

For the update in 2014 the authors CCRS and CB re-extracted data from all of the included studies and provided full assessments of the risk of bias. We compared the evaluations, and if there had been any inconsistencies we would have and discussed and resolved them.

We expanded the methods section to comply with current conduct and reporting standards for systematic reviews, including the 'Methodological Expectations of Cochrane Intervention Reviews' (MECIR). The methods were implied in previous published version of the review, but for clarity, the details are now stated explicitly. We describe how we planned to deal with assessment of risk of bias, measures of treatment effect, unit of analysis issues, dealing with missing data, assessment of heterogeneity, data synthesis, subgroup

analysis and sensitivity analysis. In our review there were too few included studies to permit assessment of reporting bias, or any sensitivity analyses.

We present results as risk ratios (RR) in the updated version of the review (previously odds ratios (OR)).

We carried out Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments of quality and present a 'Summary of findings' table that includes this assessment.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Antiemetics [\*therapeutic use]; Enteral Nutrition [\*instrumentation]; Gastric Emptying; Injections, Intravenous; Intubation, Gastrointestinal [\*methods]; Metoclopramide [\*therapeutic use]; Pylorus; Randomized Controlled Trials as Topic

### **MeSH check words**

Humans