Is metoclopramide beneficial for the post-pyloric placement of nasoenteric tubes? A systematic review and meta-analysis of randomized controlled trials

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Research

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Abstract

Background

Metoclopramide is frequently prescribed as an adjuvant for the post-pyloric placement of nasoenteric tubes (NETs). However, the efficacy and safety of metoclopramide remain controversial. The latest meta-analysis showed that metoclopramide was not beneficial in adults. Thus, this study aimed to reevaluate the effect of metoclopramide on the post-pyloric placement of NETs.

Methods

A systematic search of PubMed, Embase, the Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Wanfang data was conducted up to August 2020 for randomized controlled trials (RCTs) comparing metoclopramide with placebo or no intervention. The effect sizes of eligible studies were pooled using the relative risk (RR) and 95% confidence interval (CI) in a random-effects model. Trial sequential analysis (TSA) was used for the primary outcomes (the success rate of the post-pyloric placement of NETs).

Results

Seven eligible RCTs that included 520 participants were identified. The results of the pooled effect sizes showed that metoclopramide significantly facilitated the post-pyloric placement of NETs (RR, 1.48; 95% CI, 1.11–1.97; $P = 0.007$; $I^2 = 37\%$). However, the risk of bias assessment and the TSA results indicated that the qualities of the RCTs and the sample sizes were insufficient to confirm the efficacy of metoclopramide. Further subgroup analysis revealed that successful post-pyloric placement was more pronounced in studies in which spiral NETs were employed (RR, 1.85; 95% CI, 1.41–2.43; $P < 0.001$; $I^2 = 0\%$). Additionally, a significant increase in the success rate was also observed for post-D1 (reaching the second portion of the duodenum or beyond), post-D2 (reaching the third portion of the duodenum or beyond), and post-D3 (reaching the fourth portion of the duodenum or beyond) placement of spiral NETs. Overall adverse events were minimal.

Conclusions

The evidence accumulated so far was not strong enough to demonstrate metoclopramide's beneficial effects on the post-pyloric placement of NETs; however, it might be effective for spiral NETs. Further high-quality, large-sample RCTs are required to elucidate the effects of metoclopramide.

Trial registration

PROSPERO CRD42019123424 (10 July 2019)

Background

Early enteral nutrition (EN) by a feeding tube as the preferred method for hospitalized patients to maintain nutritional support is widely recommended if oral intake is not possible [1–3]. The advocated EN route for those who are intractably intolerant of gastric feeding or deemed to be at high risk of aspiration is post-pyloric feeding, which favorably mitigates gastric retention, gastroesophageal reflux and aspiration pneumonia [4–7].

The establishment of post-pyloric feeding access to the duodenum or jejunum is usually attempted by the bedside placement of a nasoenteric tube (NET), especially in intensive care units. However, successful post-pyloric placement of NETs remains a tough challenge for physicians when there is limited access to equipment resources (e.g., endoscopic or fluoroscopic guidance). Thus, many studies have been dedicated to improving the success rate of post-pyloric NET placement independent of special device assistance [8–11]. Of these studies, a critical theme that has intrigued physicians is the effect of prokinetic agents as an adjuvant for the post-pyloric placement of NETs [12–18].

One of the popular prokinetic agents, namely, metoclopramide, which is a specific antagonist of D2 (dopamine) receptors, has been frequently introduced in procedures of post-pyloric placement. However, controversy exists regarding the effect of metoclopramide. The latest meta-analysis of randomized controlled trials (RCTs) performed by Silva et al. concluded that metoclopramide was not beneficial in the post-pyloric placement of NETs in adults [19]. Conversely, a recent large-sample RCT conducted by Hu et al. strongly suggested that metoclopramide could improve the success rate of post-pyloric placement [18]. Although Silva's meta-analysis was well designed and strictly performed, the authors did not include Hu's study, which was published several months after their work was published. Eventually, only four RCTs [12–15] published in the last century were included in their meta-analysis. Additionally, the overall quality of evidence given by Silva's findings was very low, which indicated that the true effect of metoclopramide was likely to be substantially different from the estimate of the effect. There remains a possibility that other nonincluded studies may also be eligible for the meta-analysis.

Therefore, an updated meta-analysis was performed to reevaluate the effect of metoclopramide on the post-pyloric placement of NETs by formulating novel search strategies and using the updated databases to find additional potential studies.

Methods

The present study adhered to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline for performing and reporting [20]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42019123424).

Search strategy

We systematically retrieved studies from inception to August 2020 from electronic databases, including PubMed, Embase, the Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure

(CNKI) (www.cnki.net), and Wanfang data (www.wanfangdata.com.cn), to identify RCTs that examined the effect of metoclopramide on the post-pyloric placement of NETs. No language or publication date limitations were made to be as sensitive as possible. A hand search of the reference lists from trials located by electronic searches was performed to identify other potentially eligible studies. We also identified additional studies by contacting investigators and specialists in the field. Details of the search strategy are available in the Additional file 1.

Study selection

Studies with the following criteria were included: (1) RCTs comparing metoclopramide with placebo or no intervention for the placement of NETs irrespective of publication status, language or blinding; (2) RCTs with parallel design; (3) adults (over 18 years of age) receiving parenteral metoclopramide for the introduction of NETs; and (4) studies that provided sufficient data on baseline and final measures of the success rate of post-pyloric placement in the metoclopramide and control groups. The exclusion criteria were as follows: (1) observational studies, review articles or meta-analysis; (2) duplicated data; (3) studies examining metoclopramide in combination with other prokinetic agents; and (4) studies that lacked the necessary information for the methodology or results.

Data extraction

Two reviewers (BH and ZH) independently extracted data from each study to obtain the following information: first author's name, publication date, study location, mean age and gender of participants, sample size in each group, study design, the timing and dosage of metoclopramide, the type of NETs, confirmation of post-pyloric feeding tube location, follow-up period after initial placement, success rate of placement, and adverse events in the metoclopramide and control groups. We also attempted to contact the corresponding author by email to acquire the necessary data if not reported in articles. If we encountered a multiarmed study, we planned to use data only from the metoclopramide arm versus the placebo or no-intervention arms. All discrepancies were rechecked, and a consensus was achieved by discussion with a third author (CC).

Types of outcome measures

The primary outcome of this study was the success rate of the post-pyloric placement of NETs, which was defined as the migration of the tube tip through the pylorus and into the duodenum or jejunum, as confirmed by abdominal or chest radiography. An overall and comprehensive evaluation of 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 was analyzed as a secondary outcome. Adverse events involving drug side effects and tube insertion complications were also analyzed.

Quality assessment

The methodological quality of the included studies was independently evaluated by two reviewers (BL and CS) using the Cochrane Risk of Bias tool [21], which consists of 7 criteria to assess the risk of bias:

random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Each aforementioned item could be graded “high risk”, “low risk” or “unclear”.

Statistical analysis

The analysis was performed based on the intention-to-treat method. All studies were pooled in reporting the same primary outcomes, secondary outcomes, or adverse events together. Given that the outcomes we targeted were presented as dichotomous data, we calculated the relative risk (RR) and 95% confidence interval (CI) for each outcome with the random-effects model. Statistical analyses were performed using Review Manager 5.3 Software (The Cochrane Collaboration, Copenhagen, Denmark) and Stata 12.0 software (Stata Corp, College Station, Texas). A *P* value less than 0.05 was considered statistically significant.

We assessed the clinical heterogeneity by exploring the clinical and methodological characteristics of the included studies. The statistical heterogeneity between studies was quantified by the Chi^2 test, with an α of 0.05 used for statistical significance and I^2. I^2 values < 30, 30–59, 60–75, and > 75% were classified as low, moderate, substantial, and considerable heterogeneity, respectively [22]. Prespecified subgroup analyses for metoclopramide dosage (10 mg vs. 20 mg), the timing of medication (prior to insertion vs. after insertion), the type of feeding tube tip (spiral vs. straight) and the number of centers (single-center vs. multicenter) were used to identify the possible influence of covariates on our primary outcomes. Additionally, we also performed sensitivity analyses to examine the robustness of primary outcomes by changing to a fixed-effect model and excluding studies having a high risk of bias, published in the last century, involving less than 20 patients, or having a weight of less than 2%. We visually inspected the potential publication bias with graphical (Begg’s funnel plot) [23] and statistical tests (Egger’s test) [24].

Trial sequential analysis

Trial sequential analysis (TSA) is a method combining an a priori information size calculation for a meta-analysis with a threshold of statistical significance to evaluate the accumulated evidence [25]. We performed a TSA of metoclopramide vs. placebo or no intervention for primary outcomes to control for the risks of type (false-positive) and type (false-negative) errors due to sparse data and repetitive testing of accumulating data [26, 27]. If the cumulative Z-curve crosses the threshold boundaries, the evidence obtained in this meta-analysis is sufficient for the proof of metoclopramide’s beneficial effects, and no further RCTs are required. However, the evidence is insufficient to reach a conclusion if the cumulative Z-curve does not cross any boundary [26]. The TSA software (version 0.9.5.9 Beta; Copenhagen Trial Unit, Copenhagen, Denmark) was applied to evaluate the reliability of the meta-analyses and to determine whether the current meta-analysis sample size was sufficiently large with the following assumptions: the control event proportion calculated from the included studies; a relative risk reduction (RRR) of -20% for primary outcomes; an α of 0.05 (two sided); and a power ($1 - \beta$) of 80%.

Grading quality of evidence

Two investigators (XOY and RQ) independently used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Guideline Development Tool (GRADEpro; McMaster University 2014, Hamilton, Canada) to evaluate the quality of evidence for each outcome. The quality of evidence was stratified into four grades, namely, high, moderate, low, or very low, according to risk of bias, inconsistency, indirectness, imprecision and publication bias.

Results

Study characteristics

A total of 771 articles were screened, 29 were identified for full-text review, and 7 met the pre-specified eligibility criteria and were included (Fig. 1, Additional file 2). The summarized characteristics of the included RCTs comprising 520 patients are presented in Table 1. These studies were conducted in the USA [12–16] and China [17, 18] between 1984 and 2015, of which 5 studies were published in the last century [12–16]. In total, 520 participants were enrolled in these studies, of whom 267 were randomly assigned to the metoclopramide group and 253 to the control group. The mean age of the participants ranged from 46 to 67.6 years old. The follow-up period to confirm the tube location by abdominal or chest radiography varied from 30 minutes to 24 hours after insertion. The method of metoclopramide administration was intravenously or intramuscularly given at a dose of 10 to 20 mg prior to or after insertion. The largest sample size in the included studies was 199 [18], along with the minimum sample size of 10 [12]. Straight NETs were employed in 5 studies [12–16], and spiral NETs were introduced in another 2 studies [17, 18].

Risk of bias assessment

The risk of bias of the included studies is shown in Additional file 3, 4 and 5. All studies were rated as having a low or unclear risk of selection bias. In this domain, Hu's study generated the allocation sequence by computer and 3 studies [12, 13, 16] by a random number table. The others did not describe the allocation methods used and simply indicated that the participants were randomized. None described the method of allocation concealment except Hu's study, which performed this by telephone verification with the randomization center. For blinding, 3 studies were rated [12, 15, 18] as having a high risk of performance bias due to not having a double-blind design, and 2 studies [12, 15] were rated as having a high risk of detection bias, considering that the outcome assessors were not blinded to the treatment protocol. Of these studies, Kittinger's study was described as double-blind; however, the full details of how this was achieved were not given in the published report. Additionally, Chen's study did not provide detailed information on whether the study was designed as double-blind. Therefore, it is unclear whether participants, personnel, and outcome assessors were adequately blinded in Kittinger and Chen's studies. Hu's study was an open-label trial; however, to minimize potential bias, the tube tip position confirmed by abdominal radiography was reviewed by an expert group of intensivists and radiologists blinded to this study. Thus, we rated high risk on performance bias but low risk on detection bias for Hu's study. All

studies were considered at low risk of attrition bias and reporting bias, and 5 studies [12–14, 16, 17] had an unclear risk of other potential bias due to a lack of sample size calculations.

Primary outcome

Data from 7 studies comparing the success rate of the post-pyloric placement of NETs between the metoclopramide and control groups with a total of 520 participants were available. When we pooled the data together, the metoclopramide group showed a significant increase in the success rate of the post-pyloric placement of the NETs compared with that of the control group (RR, 1.48; 95% CI, 1.11–1.97; P = 0.007). The I^2 value of 37% indicated moderate statistical heterogeneity (Fig. 2).

The results were robust to multiple sensitivity analyses, including changing to a fixed-effect model and excluding studies having a high risk of bias, published in the last century, involving less than 20 patients, or having a weight of less than 2% (Additional file 6). Visual inspection of the funnel plot indicated no evidence of asymmetry in the effect of metoclopramide on post-pyloric placement (Additional file 7), as confirmed by Egger's regression test (P = 0.605).

However, the TSA provided the required information size of 3319 for the primary outcomes in this meta-analysis (information deficit 2799) (Fig. 3). Additionally, the cumulative Z-curve only crossed the conventional boundary, which indicated that the evidence was insufficient to reach a conclusion that metoclopramide is beneficial for the post-pyloric placement of NETs, and further high-quality, large-sample RCTs are required.

Further subgroup analysis was performed to determine if there were important subgroup differences, in light of moderate statistical heterogeneity in the primary outcomes. The results showed significant effect sizes for studies administering 20 mg metoclopramide (RR, 1.85; 95% CI, 1.42–2.42; P < 0.001; I^2 = 0%) vs. those administering 10 mg metoclopramide (RR, 1.19; 95% CI, 0.89–1.59; P = 0.25; I^2 = 0%), studies administering metoclopramide prior to insertion (RR, 1.55; 95% CI, 1.09–2.21; P = 0.02; I^2 = 41%) vs. those administering metoclopramide after insertion (RR, 1.24; 95% CI, 0.80–1.91; P = 0.34), studies employing a spiral tube (RR, 1.85; 95% CI, 1.41–2.43; P < 0.001; I^2 = 0%) vs. those employing a straight tube (RR, 1.20; 95% CI, 0.86–1.66; P = 0.36; I^2 = 9%), and studies with multiple centers (RR, 2.02; 95% CI, 1.40–2.91; P < 0.001) vs. those with a single center (RR, 1.33; 95% CI, 1.00–1.78; P = 0.05; I^2 = 19%). There were significant interactions between subgroups regarding metoclopramide dosage ($P_{interaction}$ = 0.03) and the type of feeding tube tip ($P_{interaction}$ = 0.04) (Table 2, Additional file 8).

Secondary outcomes

Two studies [17, 18] reported the accurate locations of the feeding tube tip in the duodenum or jejunum. In particular, the feeding tubes used in their studies were all spiral NETs. The pooled results revealed a significant effect of metoclopramide on the post-D1, post-D2, and post-D3 placement of spiral NETs except for proximal jejunum placement (Fig. 4).

Summary of adverse events

Adverse events are summarized in Fig. 5 according to 4 studies [12, 14, 17, 18] with adverse event data. Of those, 5 patients encountered drug side effects, including lethargy, dysphoria or amyostasia, and 32 patients encountered tube insertion complications, including nasal mucosa bleeding, airway misplacement, pain, nausea or vomiting. These adverse events were considered mild and resolved quickly without causing any severe consequences. The pooled results revealed the safety profile of metoclopramide for the post-pyloric placement of NETs (RR, 1.61; 95% CI, 0.87–2.99; $P = 0.13$; $I^2 = 0\%$).

Summary of findings

Table 3 shows a summary of the findings with the GRADE assessments of the overall quality of the evidence for the effect of metoclopramide on the post-pyloric placement of NETs. The evidence was graded as low for post-pyloric placement owing to a downgrade for serious risk of bias and small number of trials with relatively few participants or events; low for post-D1 and post-D3 placement owing to a downgrade for serious risk of bias and insufficient study number to assess publication bias; moderate for post-D2 placement owing to a large effect; and moderate for adverse events owing to a downgrade for serious risk of bias.

Discussion

In the present meta-analysis, we included 7 RCTs in the final analysis. Our results revealed that metoclopramide could improve the success rate of the post-pyloric placement of NETs; however, the evidence accumulated so far was insufficient. Furthermore, metoclopramide was found to facilitate the post-pyloric, post-D1, post-D2 and post-D3 placement of spiral NETs. Using metoclopramide in the short term for post-pyloric placement of NETs did not significantly increase the risk of adverse events.

As a conventional prokinetic agent, metoclopramide has a significant effect on the increase in antral contraction amplitude and the improvement of gastrointestinal peristalsis [13]. Therefore, in theory, metoclopramide should be beneficial for the passage of NETs through the stomach and into the duodenum or jejunum. Unfortunately, neither Silva's meta-analysis nor our results demonstrated the efficacy of metoclopramide, even though three RCTs were newly included in this updated meta-analysis. Several clinical heterogeneity deriving from participants (e.g., age, comorbidities, and concomitant medication) [28–30], operators (e.g., years of training, profession status, and educational degree of operators) [15, 31], intervention (e.g., the timing of medication, the dosage of metoclopramide, and the type of feeding tube) [12–18], outcome assessment (e.g., the follow-up period and the assessment personnel) [12–18] and the like, as well as insufficient sample sizes, may be liable for failing to establish metoclopramide's beneficial effects.

In further subgroup analyses, we found that the administration of 20 mg metoclopramide had a significantly higher success rate of post-pyloric placement than did the administration of 10 mg

metoclopramide. Although both 10 mg and 20 mg metoclopramide are plausible according to drug instruction, there has been a suggestion that metoclopramide displays disposition dose-dependency and obeys linear kinetics in individuals with intravenous or oral doses from 5 mg to 20 mg [32, 33]. Additionally, we found that the administration of metoclopramide prior to insertion could facilitate post-pyloric placement, while the interaction between subgroups did not reach statistical significance. Active gastric peristalsis at the time of feeding tube insertion is a key factor in achieving post-pyloric placement with metoclopramide [12]. The insignificant interaction may be due to only one study that administered metoclopramide after insertion. With respect to the number of centers, the multicenter RCT with a large sample size may provide a more representational result, and the insignificant interaction may be due to only one study being designated as multicenter.

Recently, a novel NET with a spiral tip for post-pyloric placement in the assistance of prokinetic agents has emerged as a promising approach [18, 34–36], as demonstrated by the subgroup results stratified by spiral or straight tube tip. In previous studies, Lai et al. demonstrated that a spiral NET in conjunction with metoclopramide is preferable to a straight NET for post-pyloric placement [37]. Additionally, a recent RCT also demonstrated the efficacy and safety of metoclopramide for the post-pyloric placement of spiral NETs [35]. The spiral design may contribute to taking full advantage of gastrointestinal peristalsis to pass the tip through the pylorus and into the duodenum and jejunum [38]. Furthermore, metoclopramide was found to facilitate the post-D1, post-D2 and post-D3 placement of spiral NETs. Thus, spiral feeding tubes may be more appropriate for post-pyloric placement if available. However, we failed to show a beneficial effect of metoclopramide on proximal jejunum placement, and there was significant between-study heterogeneity (I^2 = 62%). This may be attributed to the relatively few cases in which tube tips could spontaneously migrate to the proximal jejunum even with the aid of metoclopramide and the impaired gastrointestinal function of the critically ill patients enrolled in their studies. However, given that few studies included in this meta-analysis focused on spiral NETs, the beneficial effects of metoclopramide on post-pyloric, post-D1, post-D2, post-D3, and proximal jejunum placement warrant further investigation.

With regard to safety, concern about the use of metoclopramide has been expressed because of its potential role in causing adverse events [18]. Some investigators felt an increase in dose to 20 mg intravenously would run the risk of an increased incidence of side effects. However, the adverse events participants encountered were minimal and mild with no need for special treatment. Additionally, our results showed that there was no significant difference between the metoclopramide and control groups either in drug side effects or tube insertion complications. Therefore, metoclopramide may be safe in a regular dose of no more than 20 mg in the short term for the post-pyloric placement of NETs when more attention has been paid to its contraindications (e.g., patients in epilepsy and renal or liver dysfunction) to avoid severe adverse events.

Although this meta-analysis did not demonstrate metoclopramide's beneficial effects on the post-pyloric placement of NETs, several pivotal modifications to Silva's meta-analysis [19] had been made. First, we have included three additional studies, of which Paz's study [16] was identified by reviewing the full text after retrieving it from the English database. Chen's study [17] was retrieved from the Chinese database,

and Hu's study [18] was obtained from the updated English database. Then, this meta-analysis doubled the sample size compared with Silva's meta-analysis. Third, we have more resourceful outcome analyses, including post-D1, post-D2, post-D3 and proximal jejunum placement and adverse events involving drug side effects and tube insertion complications. Additionally, more subgroup analyses, sensitivity analyses, and publication bias were also performed for the primary outcomes. Notably, the TSA was performed to evaluate the reliability of the conclusion. Finally, we found that metoclopramide might be beneficial for the post-pyloric placement of spiral NETs. More RCTs are necessary to confirm this finding.

Additionally, there were several limitations worth noting. First, some studies were at high risk of bias, and moderate statistical heterogeneity was present in the primary outcomes, which influenced the quality of evidence and the interpretation of findings. Second, the follow-up period in the included studies was not consistent, ranging from 30 minutes to 24 hours after insertion. Third, the results of secondary outcomes and subgroup analyses might only serve as a useful hint for metoclopramide's beneficial effects on the post-pyloric placement of spiral NETs because relatively few studies provided accurate locations of the feeding tube tip. Finally, the overall quality of the evidence was low; thus, the negative results of metoclopramide for post-pyloric placement should be considered with caution.

Conclusions

In conclusion, the present meta-analysis indicated that the evidence accumulated so far was not strong enough to demonstrate metoclopramide's beneficial effects on the post-pyloric placement of NETs; however, it might be effective for spiral NETs. The findings may provide better insights into the effect of metoclopramide and help in developing an alternative approach for post-pyloric placement. In the future, to elucidate the effects of metoclopramide, it is necessary to perform high-quality, large-sample RCTs.

Abbreviations

CI
confidence interval;
CNKI
Chinese National Knowledge Infrastructure;
EN
enteral nutrition;
GRADE
Grading of Recommendations Assessment, Development, and Evaluation;
NET
nasoenteric tube;
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;
PRISMA
Preferred Reporting Items of Systematic Reviews and Meta-Analysis;
PROSPERO
International Prospective Register of Systematic Reviews;
RCT
randomized controlled trial;
RR
relative risk;
RRR
relative risk reduction;
TSA
Trial sequential analysis

Declarations

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study conception and design: YD, and CC. Literature search, study selection, and grading quality of evidence: XOY and RQ. Data extraction: BH and ZH. Quality assessment: BL and CS. Data analyses: XOY, YW, and FY. Drafting of the manuscript: XOY, and RQ. Study supervision: CC. All authors contributed important intellectual content during manuscript revision and approved the final version of the manuscript.

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Tables

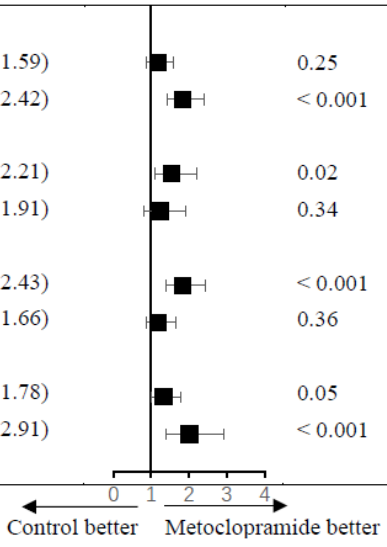
Table 1 Characteristics of included studies

Author	Country	Participants	Mean age (years)	Tube tip	Metoclopramide dose and administration	Methods for confirming post-pyloric tube location	Primary outcomes	No. of subjects M/C	No. of success (%) M/C
Whatley 1984	USA	Adult	46	Straight	Metoclopramide 20 mg IV over 10 min before insertion	By abdominal X-ray within 4 hours of metoclopramide administration or insertion	Successful post-pyloric placement	5 5	4 (80.0) 0
Seifert 1987	USA	Adult	NR	Straight	Metoclopramide 20 mg in 4 ml volume IV 15 min before insertion	By abdominal radiography 4 hours after insertion	Successful post-pyloric placement	9 10	1 (11.1) 2 (20.0)
Kittinger 1987	USA	Adult	64.8	Straight	Metoclopramide 10 mg in 2 ml volume IM or IV after insertion	By plain abdominal film 1 hour after insertion	Successful post-pyloric placement	35 35	21 (60.0) 17 (48.6)
Heiselman 1995	USA	Adult	NR	Straight	Metoclopramide 10 mg IV over 10 min before insertion	By auscultation of the right upper abdominal quadrant and abdominal radiography 45 min after tube advancement	Successful post-pyloric placement	59 46	32 (54.2) 21 (45.7)
Paz 1996	USA	Adult	63.1	Straight	Metoclopramide 10 mg IV over 15 min before insertion	By chest radiograph 30 min after insertion and repeated 24 hours later	Successful post-pyloric placement and attempt	20 16	0 2 (12.5)
Chen 2009	China	Adult	67.6	Spiral	Metoclopramide 10 mg IV before insertion and again after 12 hours	By abdominal X-ray scan 24 hours after insertion	Successful post-pyloric placement	39 42	28 (71.8) 18 (42.8)
Hu 2015	China	Adult	61.7	Spiral	Metoclopramide 20 mg IV over 10 min before insertion	By abdominal X-ray scan 24 hours after insertion	Successful post-pyloric placement	100 99	55 (55.0) 27 (27.3)

IV intravenously, *IM* intramuscularly, *NR* not reported, *M* metoclopramide group, *C* control group

Table 2 Subgroup analyses for primary outcomes

Subgroups	No. of studies	No. of subjects	RR (95% CI)	*P* value	I^2 value	$P_{interaction}$[a]
Metoclopramide dosage						0.03
10 mg	3	211	1.19 (0.89 − 1.59)	0.25	0%	
20 mg	4	309	1.85 (1.42 − 2.42)	< 0.001	0%	
The timing of medication						0.43
Prior to intubation	6	450	1.55 (1.09 − 2.21)	0.02	41%	
After intubation	1	70	1.24 (0.80 − 1.91)	0.34	NA	
The type of feeding tube tip						0.04
Spiral	2	280	1.85 (1.41 − 2.43)	< 0.001	0%	
Straight	5	240	1.20 (0.86 − 1.66)	0.36	9%	
No. of center						0.08
Single-center	6	321	1.33 (1.00 − 1.78)	0.05	19%	
Multi-center	1	199	2.02 (1.40 − 2.91)	< 0.001	NA	



RR relative risk, *CI* confidence intervals, *NA* not applicable

[a] *P* value for interaction between the metoclopramide group and control group

Table 3 Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with metoclopramide				
Successful post-pyloric placement	344 per 1000	509 per 1000 (382 to 677)	RR 1.48 (1.11 to 1.97)	520 (7 RCTs)	⊕⊕◯◯ Low [a,b]	
Successful post-D1 placement	298 per 1000	536 per 1000 (402 to 712)	RR 1.80 (1.35 to 2.39)	280 (2 RCTs)	⊕⊕◯◯ Low [a,c]	
Successful post-D2 placement	206 per 1000	420 per 1000 (284 to 621)	RR 2.04 (1.38 to 3.02)	280 (2 RCTs)	⊕⊕⊕◯ Moderate [a,c]	
Successful post-D3 placement	135 per 1000	270 per 1000 (163 to 445)	RR 2.00 (1.21 to 3.30)	280 (2 RCTs)	⊕⊕◯◯ Low [a,c]	
Successful proximal jejunum placement	121 per 1000	142 per 1000 (48 to 420)	RR 1.18 (0.40 to 3.48)	280 (2 RCTs)	⊕◯◯◯ Very Low [a,c,d]	
Adverse events	90 per 1000	144 per 1000 (51 to 177)	RR 1.61 (0.87 to 2.99)	309 (4 RCTs)	⊕⊕⊕◯ Moderate [a]	

GRADE Working Group grades of evidence: **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect; **Moderate quality:** We are moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); **Low quality:** Our confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect); **Very low quality:** We have very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect).

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, *CI* confidence interval, *RR* relative risk

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[a] The quality of evidence was downgraded one level because of serious risk of bias (no blinding of participants or personnel or outcome assessors)

[b] The quality of evidence was downgraded one level because of small number of trials with relatively few participants or events

[c] The quality of evidence was downgraded one level because of insufficient number of studies to assess publication bias using funnel plots

Figures

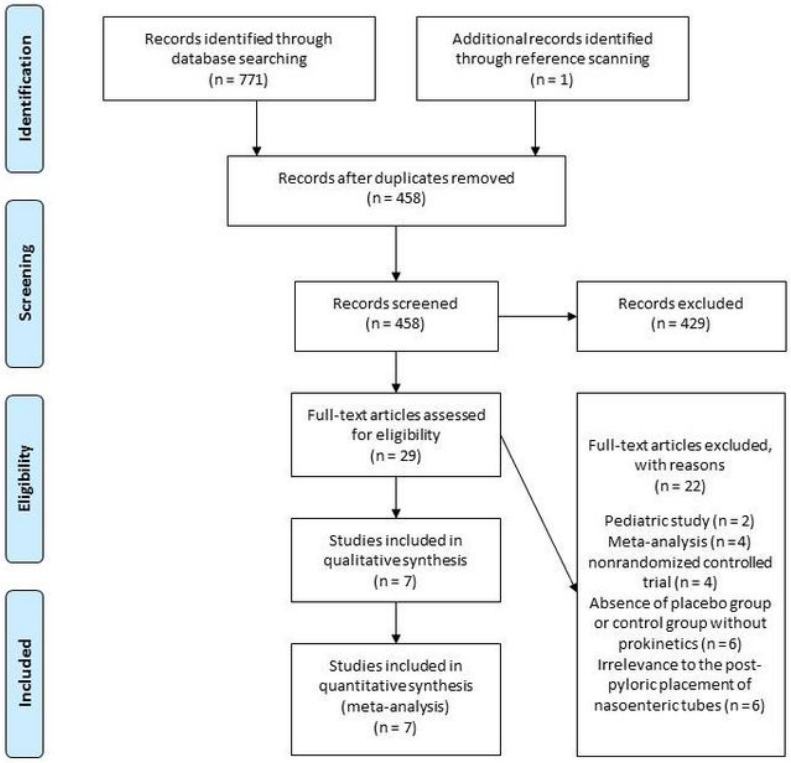


Figure 1

PRISMA flow diagram of study selection Legends: PRISMA Preferred Reporting Items of Systematic Reviews and Meta-Analysis

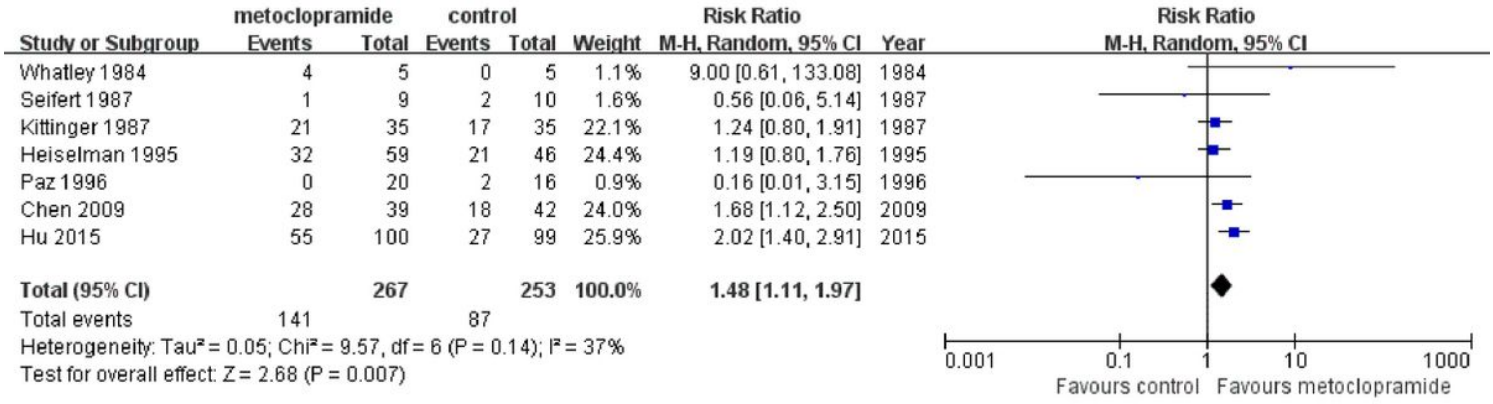


Figure 2

The effect of metoclopramide on post-pyloric placement of NETs Legends: NET nasoenteric tube

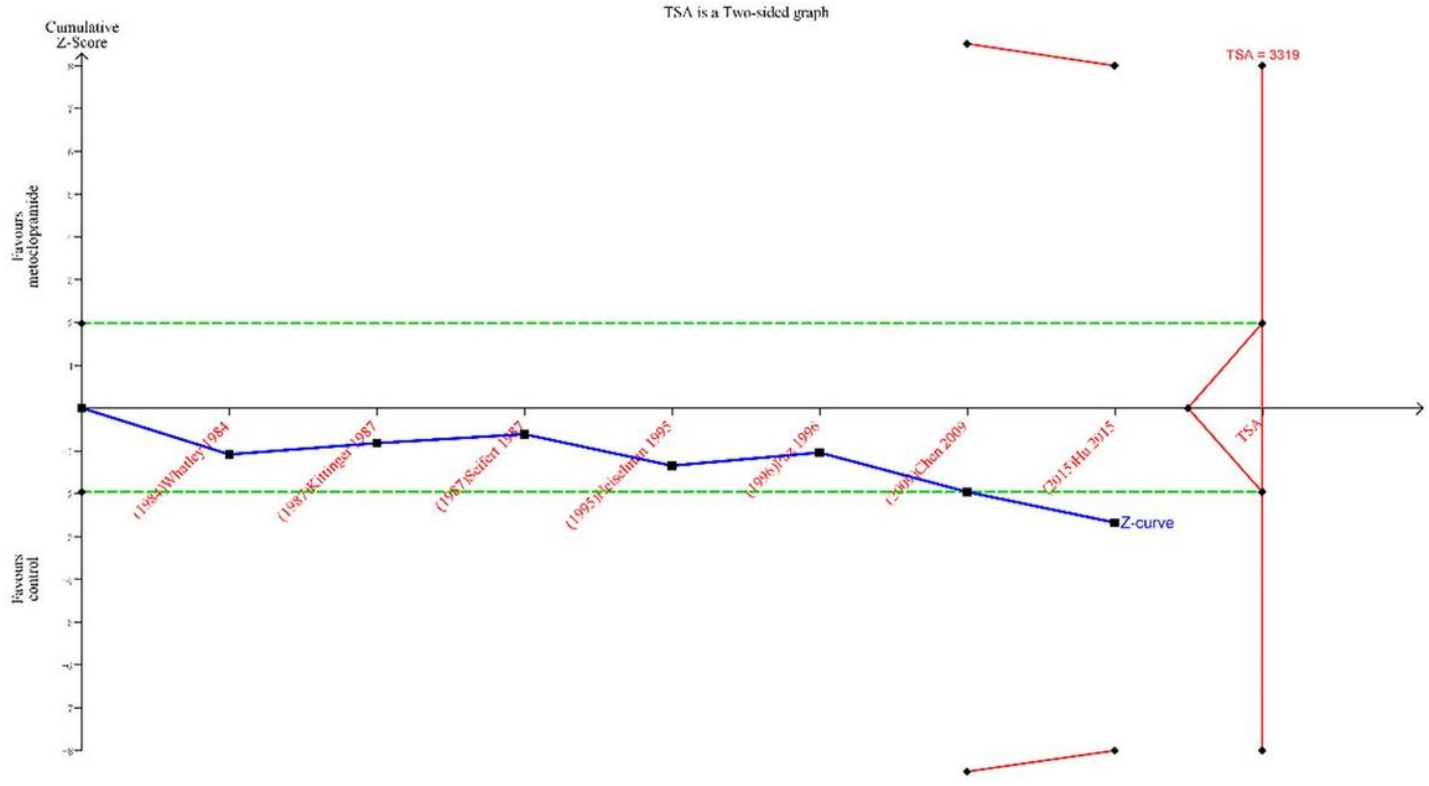


Figure 3

TSA for comparison of the success rate of post-pyloric placement of NETs between the metoclopramide group and control group Legends: The red line represents the trial sequential monitoring boundaries for benefit and the futility boundaries. The blue line is the cumulative Z-curve. The green dotted lines are conventional P = 0.05 lines. The required sample size for a conclusive result was 3319. TSA Trial sequential analysis, NET nasoenteric tube

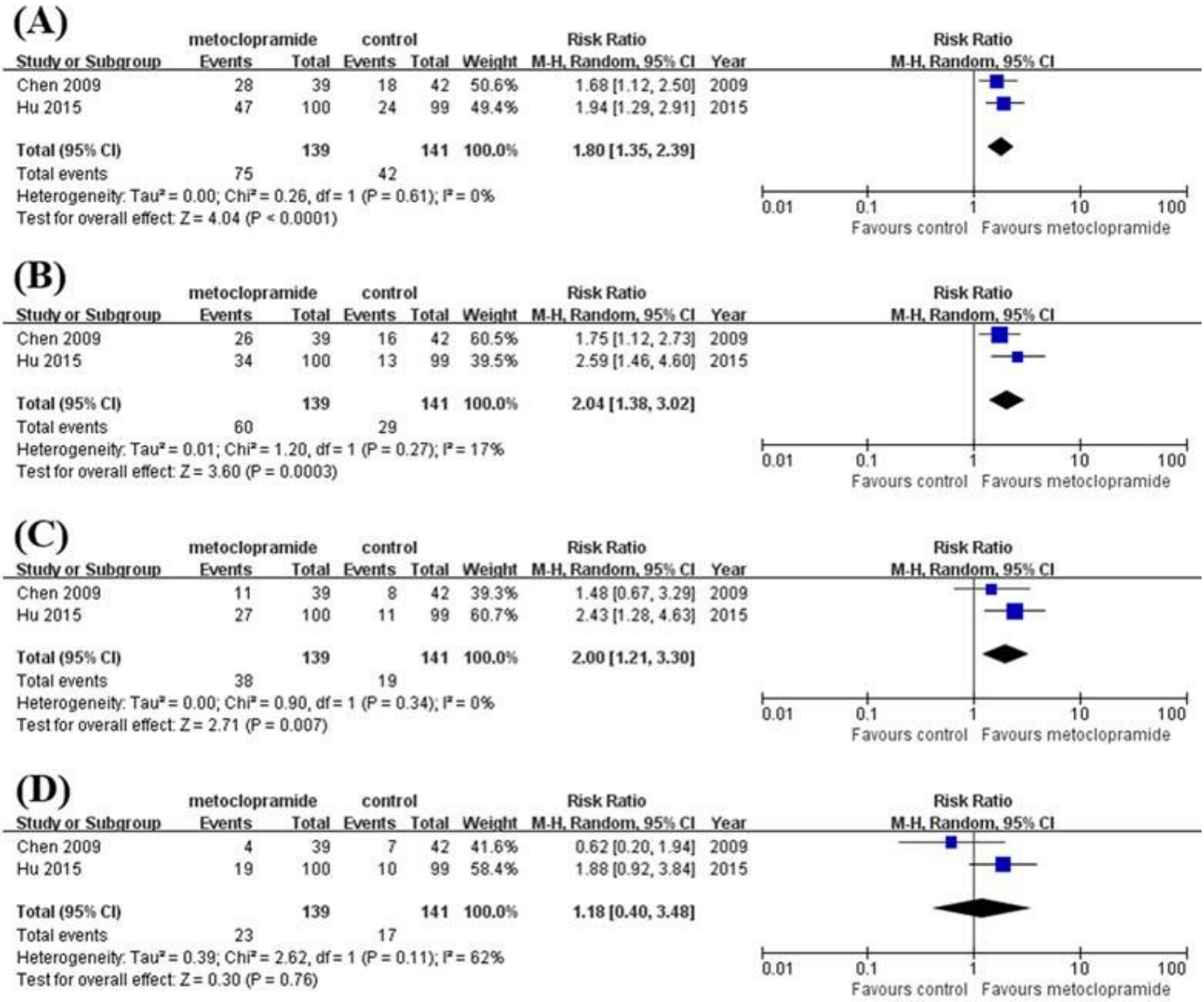


Figure 4

The effect of metoclopramide on post-D1, post-D2, post-D3 and proximal jejunum placement of NETs Legends: (A) post-D1 placement of NETs; (B) post-D2 placement of NETs; (C) post-D3 placement of NETs; (D) proximal jejunum placement of NETs. 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, NET nasoenteric tube

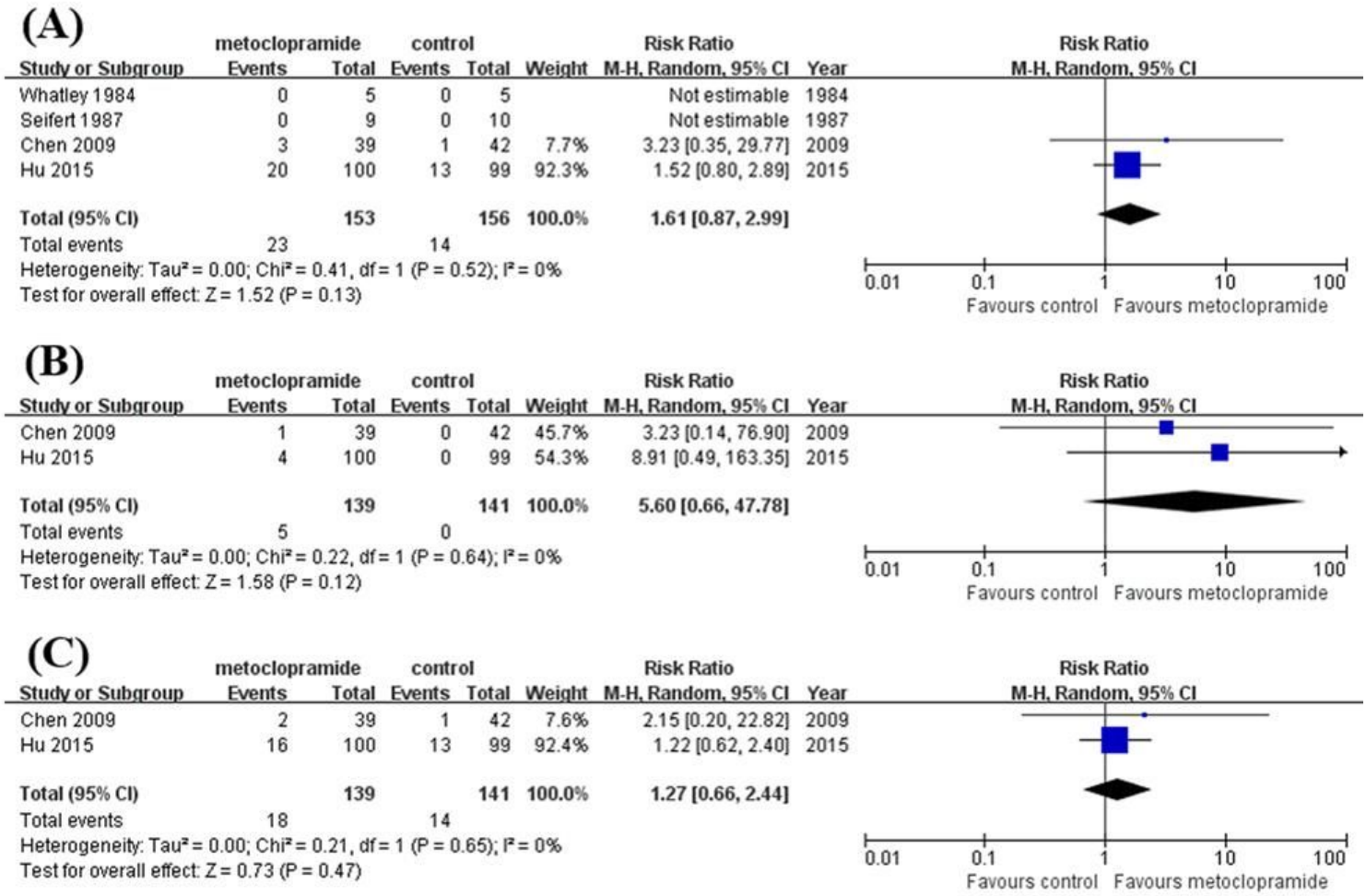


Figure 5

The comparison for adverse events between metoclopramide group and control group Legends: (A) any adverse events; (B) drug side effects; (C) tube insertion complications

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