Promotility agents for the treatment of ileus in adult surgical patients: A practice management guideline from the Eastern Association for the Surgery of Trauma

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BACKGROUND: Ileus is a common challenge in adult surgical patients with estimated incidence to be 17% to 80%. The main mechanisms of the postoperative ileus pathophysiology are fluid overload, exogenous opioids, neurohormonal dysfunction, gastrointestinal stretch, and inflammation. Management includes addressing the underlying cause and supportive care. Multiple medical interventions have been proposed, but effectiveness is uncertain. A working group of the Eastern Association for the Surgery of Trauma aimed to evaluate the effectiveness of metoclopramide, erythromycin, and early enteral nutrition (EEN) on ileus in adult surgical patients and to develop recommendations applicable in a daily clinical practice.

METHODS: Literature search identified 45 articles appropriate for inclusion. The Grading of Recommendations Assessment, Development and Evaluation methodology was applied to evaluate the effect of metoclopramide, erythromycin, and EEN on the resolution of ileus in adult surgical patients based on selected outcomes: return of normal bowel function, attainment of enteral feeding goal, and hospital length of stay. The recommendations were made based on the results of a systematic review, a meta-analysis, and evaluation of levels of evidence.

RESULTS: The level of evidence for all PICOs was assessed as low. Neither metoclopramide nor erythromycin were effective in expediting the resolution of ileus. Analyses of 32 randomized controlled trials showed that EEN facilitates return of normal bowel function, achieving enteral nutrition goals, and reducing hospital length of stay.

CONCLUSION: In patients who have undergone abdominal surgery, we strongly recommend EEN to expedite resolution of Ileus, but we cannot recommend for or against the use of either metoclopramide or erythromycin to hasten the resolution of ileus in these patients. (*J Trauma Acute Care Surg.* 2019;87: 922–934. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Type of Study Therapeutic, level II.

KEY WORDS: Ileus; metoclopramide; erythromycin; early enteral nutrition.

Ileus, a type of abnormal gastrointestinal motility, is a common phenomenon in patients who have undergone abdominal surgery. Clinical symptoms of this condition include nausea, vomiting, and absence of flatus, and/or bowel movements. The true incidence is unknown but is estimated to be 17% to 80%.[1,2]

The main mechanisms of the postoperative ileus pathophysiology are fluid overload, neurohormonal dysfunction, gastrointestinal stretch and inflammation.[2] The etiology of ileus is multifactorial and includes abdominal, thoracic, and spine operations, sepsis, and disturbances of fluid-electrolyte balance.[3] A type of the abdominal surgery also plays a role in the development of the ileus with abdominal hysterectomy and appendectomy having the lowest rate, 4.1% to 6.%, while small bowel resection has the incidence of ileus as high as 19.2%.[4] Multiple medications were reported to be associated with the development of ileus such as calcium channel blockers, clonidine, antineoplastic agents, antidiarrheal/antispasmodic, phenothiazine antiemetics,

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oral iron preparations, selective serotonin reuptake inhibitor antidepressants, tricyclic antidepressants, antipsychotics, Parkinson disease medications, first generation of H1 antihistamines, muscle relaxants, atropine products.[5]

Ileus has been shown to be associated with increased risks of aspiration, pneumonia, decreased rate of enteral feeding, increased hospital length of stay (LOS), and mortality.[6–8] An analysis of the Premier's Perspective Comparative Database, a repository of US hospital administrative data, showed that the mean LOS of patients with postoperative ileus versus those without one was 11.5 days versus 5.5 days and the mean cost of the inpatient stay was US $18,877 vs. US $9,640, respectively.[4]

The management of ileus is directed toward correction of the underlying cause, fluid-electrolyte balance, and avoidance of medications associated with ileus. The Cochrane review in 2008 summarized comparison effect of 10 systematic prokinetic agents for adynamic ileus.[9] Overall, all included studies had a poor methodological quality. Usage of alvimopan was supported by six trials. Erythromycin did not show a positive effect on the ileus. Effect of Cholecystokinin-like drugs, cisapride, dopamine-antagonists (domperidone), propranolol, vasopressin, intravenous lidocaine and neostigmine was found either inconsistent or required more evidence on clinically relevant outcomes. The use of several other prokinetic agents has been proposed to hasten the resolution of ileus, including metoclopramide, naloxone, tegaserod, mitemcinal, ghrelin, prucalopride, and dexloxiglumide.[10] Few additional agents, which are not available in the United States, are considered to have a prokinetic effect: cisapride, levosulpiride, tegaserod, mosapride citrate, itopride hydrochloride, renzapride. However, their effectiveness is unclear.

The goal of this review was to evaluate the existing evidence and create recommendations regarding the routine use of metoclopramide, erythromycin, and early enteral nutrition (EEN) in surgical patients with ileus.

OBJECTIVES

The objective of this review was to evaluate the effect of metoclopramide, erythromycin, and early enteral feeding on the resolution of ileus in adult surgical patients, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[11] The GRADE is a methodology that, through standardized approach, rates a body of evidence and makes recommendations to address specific clinical questions. The Eastern Association for the Surgery of Trauma (EAST) Ileus practice management group was created on a voluntary base from EAST members. The working group discussed different agents and voted to evaluate three of the most commonly used interventions to treat ileus include metoclopramide, erythromycin, and early enteral feeding. The group aimed to perform a systematic review and create practical management guidelines regarding usage of metoclopramide, erythromycin and EEN to hasten resolution of ileus in adult surgical patients.

Adult surgical patients were defined as those patients who underwent either elective or emergent abdominal surgery.

Through an iterative voting process, the EAST Ileus practice manage management workgroup developed the following PICO questions (Population, Intervention, Comparison, Outcomes):

PICO 1

In adult surgical patients (P) with ileus, should treatment with metoclopramide be instituted (I), versus usual care without metoclopramide (C), to accelerate return of normal bowel function and attainment of enteral feeding goal, and to decrease hospital LOS?

PICO 2

In adult surgical patients (P) with ileus, should treatment with erythromycin be instituted (I), versus usual care without erythromycin (C), to accelerate return of normal bowel function and attainment of enteral feeding goal, and to decrease hospital LOS?

PICO 3

In adult surgical patients (P) with ileus, should early enteral feeding (defined as enteral nutrition that was started during the first 48 hours after the surgery) be instituted (I), compared with usual care (C), to accelerate return of normal bowel function and attainment of enteral feeding goal, and to decrease hospital LOS?

OUTCOME MEASURE TYPE

The members of the working group proposed outcomes related to resolution of ileus. All outcomes were independently rated by each group member on a scale from 1 to 9 and the median score for each outcome was calculated and assigned as the final score.

Outcomes scored between 7 and 9 were considered critical and included: resolution of ileus, time to first flatus, time to first bowel movement, duration of nasogastric tube (NGT), NGT reinsertion rate, attainment of enteral feeding goal, and hospital LOS. The working group decided to evaluate the resolution of ileus utilizing the following outcomes: return of normal bowel function, attainment of enteral feeding goal, and hospital LOS.

The outcome "return of normal bowel function" was based on: time to first flatus, time to first bowel movement, duration of NGT and NGT reinsertion rate.

The original outcome voting also contained nutritional adequacy, tolerance of solid food, tolerance of enteral nutrition, and time to achieve goal enteral nutrition. Given the significant heterogeneity in the measurement of goal enteral feeding among studies, the above outcomes were combined into the "attainment of enteral feeding goal" outcome, which was deemed as a critical outcome.

IDENTIFICATION OF REFERENCES

A medical librarian performed a search of citations in the following databases: PubMed, CINAHIL, Embase, Cochrane Library, Web of Science, PROSPERO, RefWorks, and Scopus. The search was performed using the following MeSH terms: "Ileus," "Metoclopramide", "Erythromycin", "Metoclopramide", "Reglan", "Metozolv", "Maxolon," "Rimetin," "Rimperan", "Cerucal", "Erythromycin, "Trophic", "Early enteral"," Early enteral feeding," "Early enteral hypocaloric," "Gut priming," "Minimal enteral," "Minimal enteral feeding," "Minimal enteral feeds," "Minimal enteral intake," and "Minimal enteral nutrition."

Original clinical retrospective studies, prospective observational studies, and randomized controlled trials (RCT) in adults

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(age, ≥18 years) were considered for inclusion. Review articles, meta-analyses, case reports, case series without a comparison group, manuscripts that evaluated colonic pseudo-obstruction, and non-English language publications were excluded.

Two members of the working group independently screened titles and abstracts of the selected references removing obviously irrelevant reports. Next, full-text articles were independently screened by two separate working group members, aiming to include reports that were in compliance with a priory chosen eligibility criteria. Selected studies were included for final data extraction and analysis. At each stage of the screening process, disagreements between the reviewers were adjudicated by discussion and consensus among the individuals. When consensus was not reached, a third reviewer was involved as an arbitrator (Fig. 1).

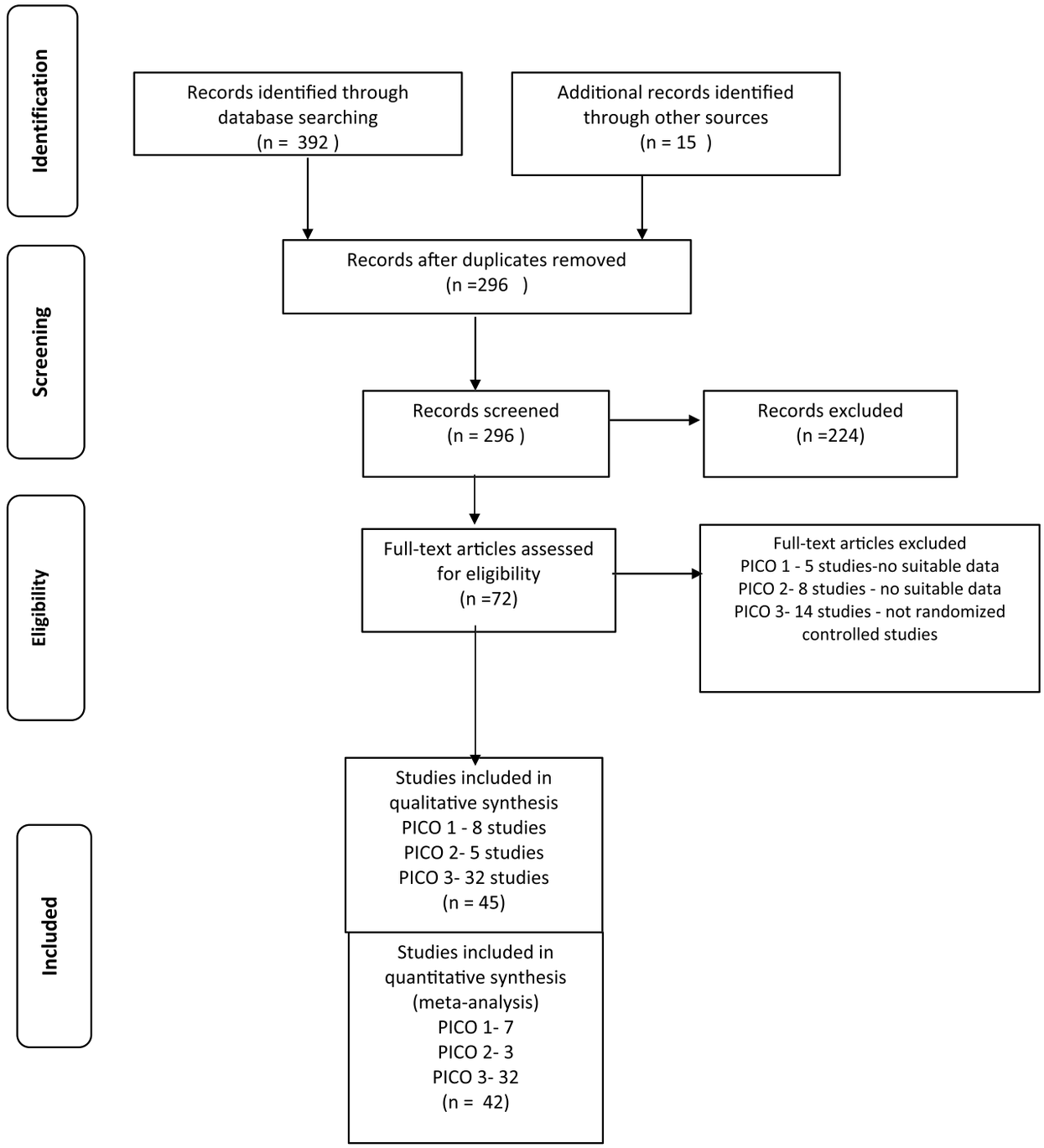

Figure 1. PRISMA flow diagram for study selection.

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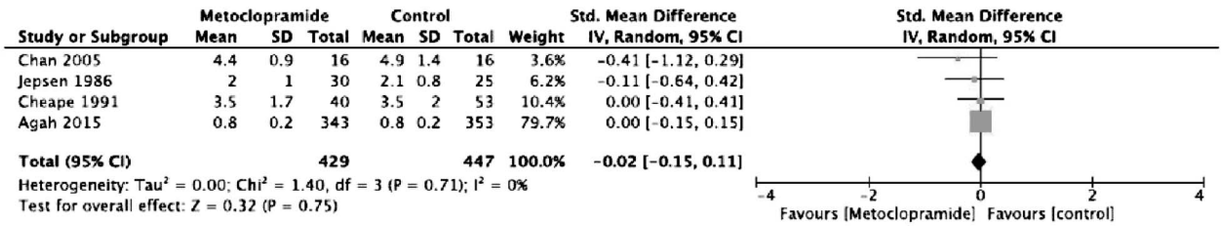
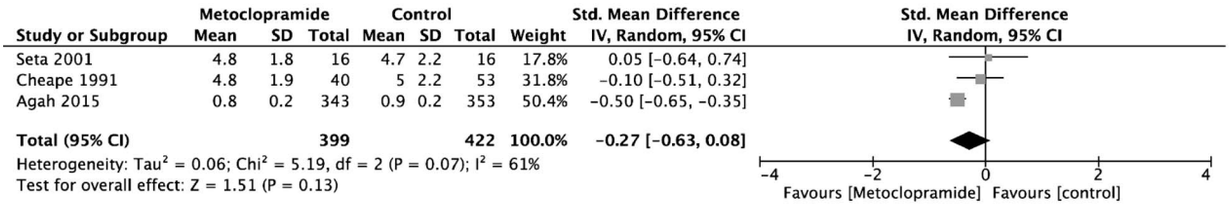
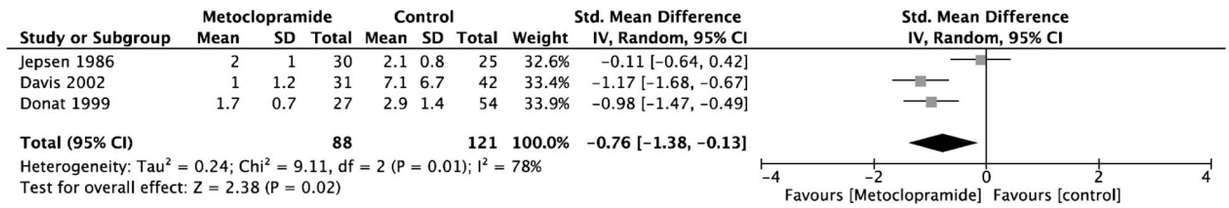
A **Time to the first flatus**



B **Time to the first bowel movement**



C **Duration of nasogastric tube**



D **Rate of nasogastric tube reinsertion**

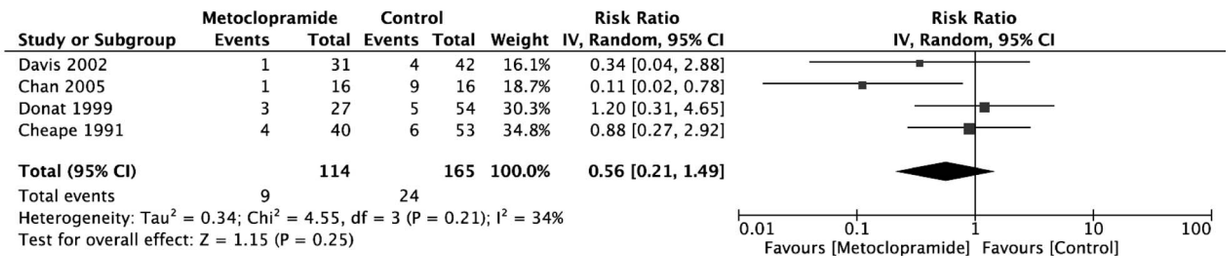


Figure 2. Metoclopramide. A, Time to the first flatus. B, Time to the first bowel movement. C, Duration of NGT. D, Rate of NGT reinsertion. E, Attainment of goal enteral feeding. F, Hospital LOS.

DATA EXTRACTION AND METHODOLOGY

A total of 45 studies were included.[12–56] Data extraction was performed by two independent team members for each of the selected studies and entered into a Microsoft Excel 2010 (Redmond, WA) spreadsheet. The meta-analysis and creation of forest plots was performed using Review Manager (RevMan) (Version 5.3; Cochrane Collaboration, Oxford). Dichotomous outcomes were reported as risk ratio (RR), and continuous variables were reported as standardized mean difference (SMD). Confidence interval (CI) of 95% was presented with RR and SMD. For studies that reported continuous variables as median and range[15,18,20,23,24,41,46,47,49,50,54] means and standard deviations were estimated in order to be able to perform the meta-analysis.[57]

All time-related outcomes were presented in days.

RISK OF BIAS

Risk of bias of the included RCT was assessed in six domains: sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and "other issues" (Supplemental Digital Content

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TABLE 1. Assessment of Evidence

	Certainty assessment						No. patients		Effect			
No. Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Metoclopramide	Usual Care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Return of normal bowel function: first Flatus (days)												
4	Randomized trials[a]	Not serious	Serious[b]	Not serious	Serious[c]	None	429	447	—	SMD, 0.02 SD lower (0.15 lower to 0.11 higher)	⊕⊕○○ LOW	CRITICAL
Return of normal bowel function: 1st Bowel movement (days)												
3	Randomized trials[d]	Not serious	Serious[b]	Not serious	Serious [c]	None	399	422	—	SMD, 0.27 SD lower (0.63 lower to 0.08 higher)	⊕⊕○○ LOW	CRITICAL
Return of normal bowel function: NGT duration												
3	Observational studies[e]	Not serious	Not serious	Not serious	Serious[f]	None	88	121	—	SMD, 0.76 SD lower (1.38 lower to 0.13 lower)	⊕○○○ VERY LOW	CRITICAL
Return of normal bowel function: NGT reinsertion												
4	Observational studies[g]	Not serious	Not serious	Not serious	Not serious	None	9/114 (7.9%)	24/165 (14.5%)	RR, 0.56 (0.21 to 1.49)	64 fewer per 1,000 (from 115 fewer to 71 more)	⊕⊕○○ LOW	CRITICAL
Attainment of enteral feeding goal												
6	Observational studies[h]	Not serious	Serious	Not serious	Serious[b]	None	473	534	—	SMD, 0.03 SD lower (1.27 lower to 1.21 higher)	⊕○○○ VERY LOW	CRITICAL
LOS												
3	Observational studies[i]	Not serious	Not serious	Not serious	Serious[b]	None	74	112	—	SMD, 0.42 SD lower (0.72 lower to 0.12 lower)	⊕○○○ VERY LOW	CRITICAL

B

	Certainty assessment						No. patients		Effect			
No. studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erythromycin	Usual care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Return of normal bowel function: 1st Flatus, d												
3	Randomized trials	not serious	not serious	not serious	very serious [a]	none	117	115	—	SMD, 0.19 SD lower (0.45 lower to 0.07 higher)	⊕⊕○○ LOW	CRITICAL
Return of normal bowel function: 1st Bowel movement, d												
2	Randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	106	105	—	SMD, 0.05 SD lower (0.32 lower to 0.22 higher)	⊕⊕○○ LOW	CRITICAL
Return of normal bowel function: duration of NGT												
3	Randomized trials	Not serious	Not serious	Not serious	Very serious [a,b]	None	There were total of 87 patients who received erythromycin (intervention) as a treatment for the postoperative ileus and 90 patients who did not (control). All studies reported statistical results differently, not allowing to perform meta-analysis. All studies reported no statistical difference of duration of NGT between the intervention and control groups.				⊕⊕○○ LOW	CRITICAL
Attainment of enteral feeding goal												

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2	Randomized trials	Not serious	Not serious	Very serious [c]	Very serious [a,b]	None	106	105	—	SMD, 0.05 SD higher (0.22 lower to 0.32 higher)	⊕○○○ VERY LOW	CRITICAL
Hospital LOS												
3	Randomized trials	Not serious	Not serious	Not serious	Very serious [a,b]	None	117	115	—	SMD, 0.05 SD higher (0.23 lower to 0.34 higher)	⊕⊕○○ LOW	CRITICAL

C

	Certainty assessment						No. patients		Effect			
No. studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early Enteral Feeding	Usual Care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Return of normal bowel function: 1st Flatus												
19	Randomized trials	Not serious	Serious[a]	Not serious	Not serious [b,c]	None	1404	1423	—	SMD, 0.99 SD lower (1.4 lower to 0.58 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Return of normal bowel function: first bowel movement												
20	Randomized trials	Not serious	Serious [a]	Not serious	Serious [b,c]	None	1731	1737	—	SMD, 0.91 SD lower (1.3 lower to 0.52 lower)	⊕⊕○○ LOW	CRITICAL
Return of normal bowel function: NGT duration												
3	Randomized trials	Not serious	Not serious	Not serious	Serious [c]	None	178	186	—	SMD, 1.09 SD lower (1.88 lower to 0.3 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Return of normal bowel function: NGT reinsertion												
8	Randomized trials	Not serious	Very serious[a]	Not serious	Serious [b,c]	None	61/524 (11.6%)	50/530 (9.4%)	RR, 1.24 (0.84 to 1.83)	23 more per 1,000 (from 15 fewer to 78 more)	⊕○○○ VERY LOW	CRITICAL
Attainment of enteral feeding goal												
15	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	1020	1028	—	SMD, 2.61 SD lower (3.37 lower to 1.85 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Hospital LOS												
29	Randomized trials	Not serious	Serious[a]	Not serious	Serious[b,c]	None	2028	2044	—	SMD, 0.8 SD lower (1.1 lower to 0.5 lower)	⊕⊕○○ LOW	CRITICAL

[a] Three RCT and one prospective with a control group studies.
[b] The included studies showed inconsistent effect of metoclopramide on the outcome.
[c] The results of two of the included studies have wide confidence intervals.
[d] Two randomized controlled studies and one prospective with a control group study.
[e].One retrospective study with a control group, one prospective study with a control group and one randomized control trial.
[f] The results from one out of three included studies showed wide confidence interval.
[g] One retrospective, two prospective studies with control groups, and one randomized control trial.
[h] One retrospective, three prospective, and two RCTs.
[i] One retrospective, and two prospective studies with control groups.
Table 2
a. All included studies showed results with wide confidence intervals.
b. Small sample size studies.
c. Critically ill patients.
Table 3
a. Included studies showed opposite effect of the intervention to the outcome.
b. Included studies had wide confidence intervals.
c. Low sample size.

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1–3, Figs. 1–3, http://links.lww.com/TA/B414, http://links.lww.com/TA/B415, http://links.lww.com/TA/B416).

GRADING THE EVIDENCE

The available evidence was assessed according to the GRADE methodology as high, moderate, low, or very low quality. The quality of evidence was downgraded for inconsistency, indirectness, and imprecision.

RESULTS FOR THE USE OF METOCLOPRAMIDE (PICO 1)

In adult surgical patients (P) with ileus, should treatment with metoclopramide be instituted (I), versus usual care without metoclopramide (C), to accelerate return of normal bowel function and attainment of enteral feeding goal, and to decrease hospital LOS?

QUALITATIVE ANALYSIS

Our search yielded a total of eight studies: three RCT,[15,17,18] three prospective with control groups,[12,13,16] and two retrospective with control groups.[14,19] The included studies contained 543 patients in the intervention group and 599 in control groups. The selected studies included a heterogeneous patient population: patients requiring intensive care unit after abdominal surgeries,[10] and non-intensive care unit surgical patients who underwent abdominal operations for variety of indications.[12,14–19] Overall, included studies were heterogeneous in terms of inclusion/exclusion criteria, the dose of the intervention, and how the clinical effect of metoclopramide on the ileus was reported. Studies where metoclopramide was combined with another agent were excluded.

In only one study was metoclopramide compared with placebo.[15] In seven studies, metoclopramide was compared with no intervention: no placebo or other medication.[12–14,16–19] In one study, metoclopramide was a part of fast-track program[19]; the control arm also included the fast-track program but without metoclopramide.

Overall, five studies concluded that metoclopramide had a beneficial effect on ileus.[12,14,16,18,19] The positive metoclopramide effect was based on different criteria: return of normal bowel function: time to first bowel movement,[18] duration of NGT,[14,16] NGT reinsertion rate[12]; attainment of enteral feeding goal,[12,14,16,18] and LOS.[14] Pruthi et al.[19] concluded a positive effect of metoclopramide based on a decreased rate of nausea and vomiting, but there was no effect on the PMG-selected outcomes (return of normal bowel function and LOS).

In the studies where no positive effect was found,[13,15,17] this conclusion was based on lack of return of normal bowel function: time to first flatus,[15,17] time to first bowel movement,[13,17] NGT reinsertion rate,[17] attainment of goal enteral feeding,[13,15,17] and hospital LOS.[13]

The postoperative complication rate in the metoclopramide groups was not significantly higher in the studies that reported them.[16,19] No adverse events related to the usage of metoclopramide were reported.

QUANTITATIVE ANALYSIS (META-ANALYSIS)

Seven out of the eight studies were suitable for meta-analysis. There was a beneficial effect of metoclopramide on the duration of NGT (SMD, −0.76; 95% CI, −1.38 to −0.13), the rate of NGT reinsertion (RR, 0.56; 95% CI, 0.21–1.49), and hospital LOS (SMD, −0.42; 95% CI, −0.72 to −0.12) (Fig. 2C, 2D, 2F).

With regard to the time to first flatus, time to first bowel movement, and the attainment of enteral feeding goals, the effect of metoclopramide was uncertain (Fig. 2A, 2B, 2E).

GRADING THE EVIDENCE

The evidence was assessed applying the GRADE framework (Table 1). First, the level of evidence was decreased for all outcomes due to the inclusion of retrospective and prospective observational studies. We also downgraded the level of evidence for inconsistency due to inconsistent effect of metoclopramide on the time to first flatus, time to first bowel movement, and attainment of goal enteral feeding. Since wide confidence intervals were reported for the time to first flatus, time to first bowel movement, and attainment of goal enteral feeding, the level of evidence was further decreased for imprecision.

The bias assessment revealed that 33% of included RC had a lack of blinding of either participant or the research staff to the studies' group assignments (performance bias). Also sequence generation and allocation concealment (selection bias) was not clearly described in all included studies (Supplemental Digital Content 1, Fig. 1, http://links.lww.com/TA/B414). Because of these factors, the quality of evidence was deemed to be low.

RECOMMENDATIONS FOR THE USE OF METOCLOPRAMIDE (PICO 1)

Based on the analysis of included studies, the effect of metoclopramide on the selected outcomes, and the low level of evidence we cannot make a recommendation for or against the use of metoclopramide in adult surgical patients to hasten ileus resolution. Although the usage of metoclopramide was not associated with adverse outcomes, the effect on ileus resolution and attainment of enteral nutrition goal was inconsistent.

RESULTS FOR THE USE OF ERYTHROMYCIN (PICO 2)

In adult surgical patients (P) with ileus, should treatment with erythromycin be instituted (I), versus usual care without erythromycin (C), to accelerate return of normal bowel function and attainment of enteral feeding goal, and to decrease hospital LOS?

QUALITATIVE ANALYSIS

There were five studies selected for the analysis for PICO 2. Four studies were RCT comparing erythromycin to placebo.[20,21,23,24] We also included one prospective study with a control group[22] in which patients received erythromycin versus usual care for ileus. There were a total of 128 patients treated with erythromycin and 140 patients in the control groups.

The selected studies included patients who underwent abdominal operations for a variety of reasons.[20–24] Overall,

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included studies were heterogeneous in terms of inclusion/exclusion criteria and dose of intervention (from a few day course until oral diet was tolerated or a fixed number of days, 2 days to 7 days.[20–24] Also, the studies reported the effect of erythromycin on ileus using different parameters.

No beneficial effect of erythromycin on the resolution of ileus was found in any of the included studies. These conclusions were made based on the following: no effect on time to first flatus,[20–24] time to first bowel movement,[20,22,24] duration of NGT,[20,21,24] and tolerance of enteral diet.[20,23,24]

The postoperative complication rate in the erythromycin groups was not significantly higher in the studies that reported them.[20,21,23,24] An erythromycin-related skin rash was reported in only in four out of 106 patients.[23,24]

QUANTITATIVE ANALYSIS

Three[21,23,24] of five studies were suitable for meta-analysis (Fig. 3). The meta-analysis failed to show a beneficial effect of erythromycin on time to first flatus (SMD, −0.19; 95% CI, −0.45 to 0.07), time to first bowel movement (SMD, −0.05; 95% CI, −0.32 to 0.22), attainment of enteral feeding goal (SMD, 0.05; 95% CI, −0.22 to 0.32), or hospital LOS (SMD, 0.05; 95% CI, −0.23 to 0.34).

GRADING THE EVIDENCE

The evidence was assessed applying the GRADE framework (Table 2). The level of evidence was decreased for imprecision when results were reported with wide confidence intervals: time to first flatus, time to first bowel movement, and hospital LOS. The level of evidence was downgraded for imprecision, as all included studies had low sample sizes.

The bias assessment revealed that 75% of included RC did not describe either sequence generation or allocation concealment (selection bias). About 50% of the included studies had a lack of blinding of outcome assessment (detection bias) (Supplemental Digital Content 2, Figure 2, http://links.lww.com/TA/B415). The overall quality of evidence was assessed as low.

RECOMMENDATIONS FOR THE USE OF ERYTHROMYCIN (PICO 2)

Based on the analyses of included studies, the effect of erythromycin on the selected outcomes, and the level of evidence, we cannot make a recommendation for or against the use of erythromycin in adult surgical patients to hasten ileus resolution.

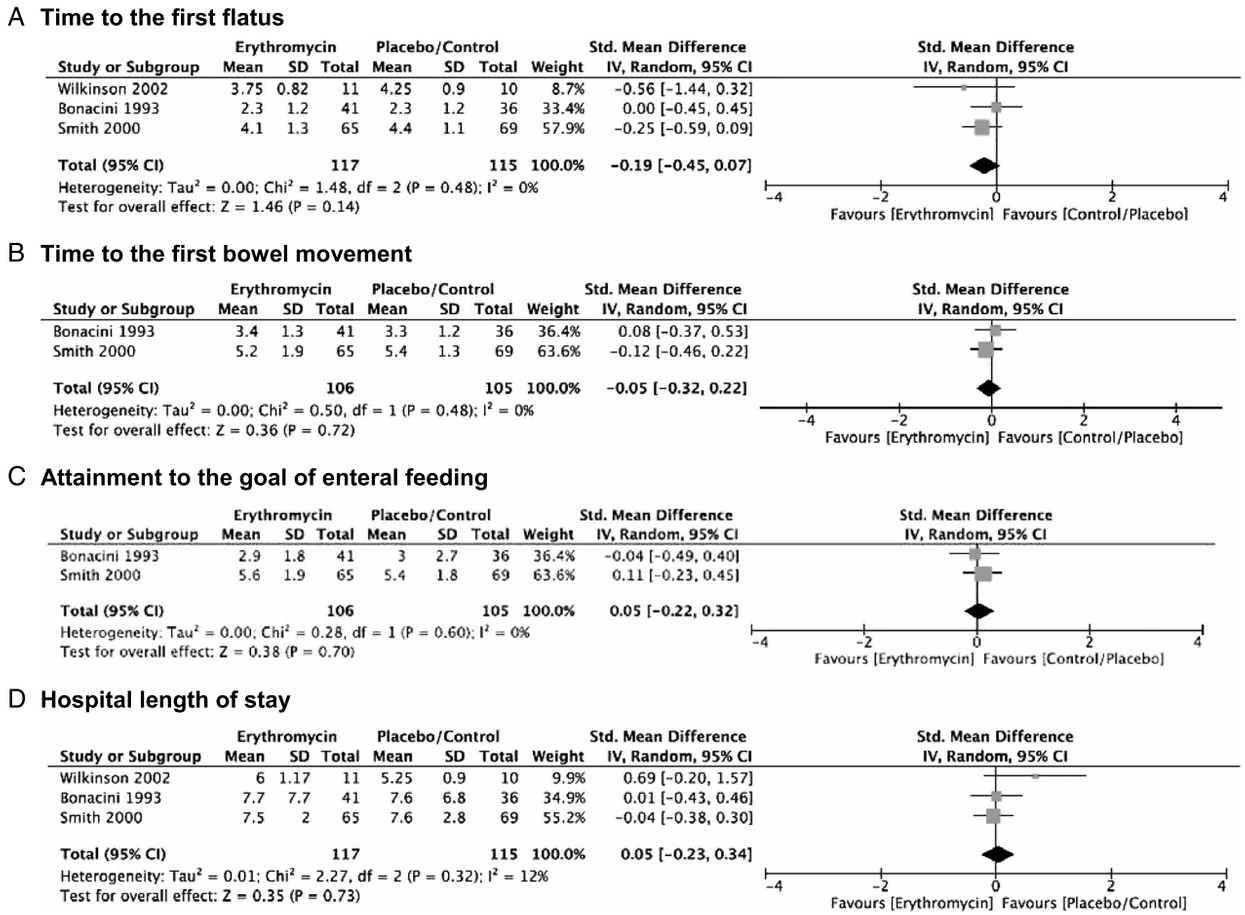

Figure 3. Erythromycin. A, Time to the first flatus. B, Time to the first bowel movement. C, Attainment to the goal of enteral feeding. D. Hospital LOS.

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RESULTS FOR THE USE OF EEN (PICO 3)

In adult surgical patients (P) with ileus, should early enteral feeding (defined as enteral nutrition that was started during the first 48 hours after the surgery) be instituted (I), compared to usual care (C), to accelerate return of normal bowel function and attainment of enteral feeding goals, and to decrease hospital LOS?

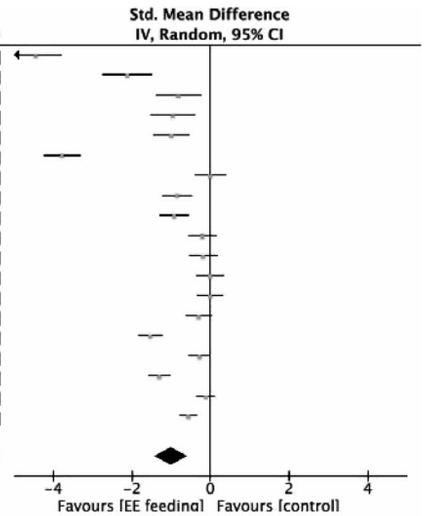
QUALITATIVE ANALYSIS

Given the large number of publications on this subject, we included only RCT. There were 32 RCT studies selected for the analysis for PICO 3.[25–56] There were a total of 2,398 patients treated with EEN, and there were 2,242 patients in the control groups.

A Time to the first flatus

Study or Subgroup	Early enteral feeding Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Mahla 2016	1.4	0.1	64	2.4	0.3	64	4.9%	−4.45 [−5.10, −3.79]
Vaithiswaran 2008	1.4	0.6	30	2.8	0.7	31	4.9%	−2.12 [−2.75, −1.48]
Fonseca 2011	1.5	0.5	24	2	0.7	26	5.0%	−0.80 [−1.38, −0.23]
Hur 2011	1.9	1.2	28	2.9	0.8	26	5.0%	−0.96 [−1.53, −0.39]
Stewart 1998	3	1	40	4	1	40	5.2%	−0.99 [−1.46, −0.52]
Orji 2009	1.9	0.1	100	2.5	0.2	100	5.2%	−3.78 [−4.25, −3.31]
Feo 2004	4	1.3	50	4	1.5	50	5.3%	0.00 [−0.39, 0.39]
Nakeeb 2009	3.3	0.9	60	4.2	1.2	60	5.3%	−0.84 [−1.22, −0.47]
Cutillo 1999	2	0.8	61	3	1.3	61	5.3%	−0.92 [−1.29, −0.55]
Balayla 2015	1.6	0.5	61	1.7	0.5	58	5.3%	−0.20 [−0.56, 0.16]
Chatterjee 2012	2.1	0.5	60	2.2	0.6	60	5.3%	−0.18 [−0.54, 0.18]
Han-Geurts 2007	2	2.3	61	2	1.5	67	5.3%	0.00 [−0.35, 0.35]
MacMillan 2000	1.2	1	67	1.2	0.9	72	5.4%	0.00 [−0.33, 0.33]
Mining 11/2009	1.9	1.1	71	2.2	0.9	72	5.4%	−0.30 [−0.63, 0.03]
Pragatheeswarane 2014	2.6	0.9	100	4.5	1.5	100	5.4%	−1.53 [−1.85, −1.21]
Pearl 1998	3.2	1.5	92	3.6	1.4	103	5.4%	−0.28 [−0.56, 0.01]
Braga 2001	2.4	1.3	126	4.6	2	131	5.4%	−1.30 [−1.56, −1.03]
Klappenbach 2013	0.9	0.8	148	1	0.9	147	5.5%	−0.12 [−0.35, 0.11]
Zhou 2006	3	0.9	161	3.6	1.2	155	5.5%	−0.57 [−0.79, −0.34]
Total (95% CI)			**1404**			**1423**	**100.0%**	**−0.99 [−1.40, −0.58]**

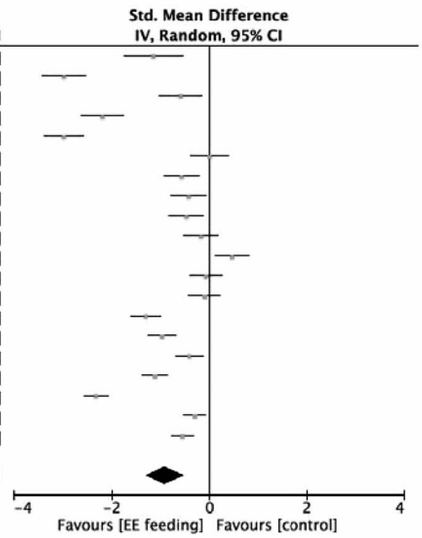
Heterogeneity: Tau² = 0.79; Chi² = 464.59, df = 18 (P < 0.00001); I² = 96%
Test for overall effect: Z = 4.73 (P < 0.00001)



B Time to the first bowel movement

Study or Subgroup	Early enteral feeding Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hosseini 2010	2.7	1.7	26	4.4	1.1	23	4.6%	−1.15 [−1.76, −0.54]
Reissman 1995	3.8	0.1	80	4.1	0.1	81	4.9%	−2.99 [−3.44, −2.53]
Stewart 1998	4	1.8	40	5	1.5	40	4.9%	−0.60 [−1.05, −0.15]
Mahla 2016	1.9	0.4	64	2.9	0.5	64	4.9%	−2.20 [−2.64, −1.75]
Orji 2009	2.4	0.2	100	3	0.2	100	4.9%	−2.99 [−3.39, −2.58]
Feo 2004	4	1.8	50	4	1.5	50	5.0%	0.00 [−0.39, 0.39]
Nakeeb 2009	4.2	1.2	60	4.9	1.2	60	5.0%	−0.58 [−0.95, −0.21]
Balayla 2015	2.7	0.5	61	2.9	0.4	58	5.0%	−0.44 [−0.80, −0.07]
Cutillo 1999	3	2.3	61	4	1.8	61	5.0%	−0.48 [−0.84, −0.12]
Chatterjee 2012	2.1	0.5	60	2.2	0.6	60	5.0%	−0.18 [−0.54, 0.18]
Han-Geurts 2007	4	2	61	3	2.3	67	5.0%	0.46 [0.11, 0.81]
MacMillan 2000	1.2	1.3	67	1.3	1.3	72	5.0%	−0.08 [−0.41, 0.26]
Mining 11/2009	5	2.3	71	5.3	3.1	72	5.0%	−0.11 [−0.44, 0.22]
Pragatheeswarane 2014	3.8	1.3	100	6.1	2.1	100	5.1%	−1.31 [−1.62, −1.01]
Dag 2011	3.4	0.8	99	4.4	1.2	100	5.1%	−0.98 [−1.27, −0.68]
Adupa 2003	2.8	1	96	3.2	0.9	96	5.1%	−0.42 [−0.70, −0.13]
Braga 2001	4.2	1.6	126	6.3	2.1	131	5.1%	−1.12 [−1.38, −0.86]
Li 2015	2.9	0.3	200	3.6	0.3	200	5.1%	−2.33 [−2.58, −2.07]
Klappenbach 2013	1.7	1.2	148	2.1	1.4	147	5.1%	−0.31 [−0.54, −0.08]
Zhou 2006	4.1	1.1	161	4.8	1.4	155	5.1%	−0.56 [−0.78, −0.33]
Total (95% CI)			**1731**			**1737**	**100.0%**	**−0.91 [−1.30, −0.52]**

Heterogeneity: Tau² = 0.77; Chi² = 546.80, df = 19 (P < 0.00001); I² = 97%
Test for overall effect: Z = 4.55 (P < 0.00001)



C Duration of nasogastric tube

Study or Subgroup	Early enteral feeding Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hosseini 2010	1.6	0.5	26	4.6	2	23	29.1%	−2.08 [−2.79, −1.38]
Chatterjee 2012	2	0.9	60	2.8	0.7	60	34.8%	−0.99 [−1.37, −0.61]
Pearl 1998	2.7	0.6	92	3.1	1.3	103	36.1%	−0.39 [−0.67, −0.10]
Total (95% CI)			**178**			**186**	**100.0%**	**−1.09 [−1.88, −0.30]**

Heterogeneity: Tau² = 0.43; Chi² = 21.46, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 2.69 (P = 0.007)

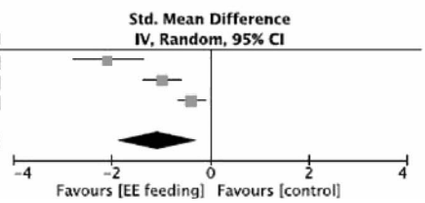


Figure 4. Early enteral nutrition. A, Time to the first flatus. B, Time to the first bowel movement. C, Duration of NGT. D, Rate of NGT reinsertion. E, Attainment to the goal of enteral feeding. F, Hospital LOS.

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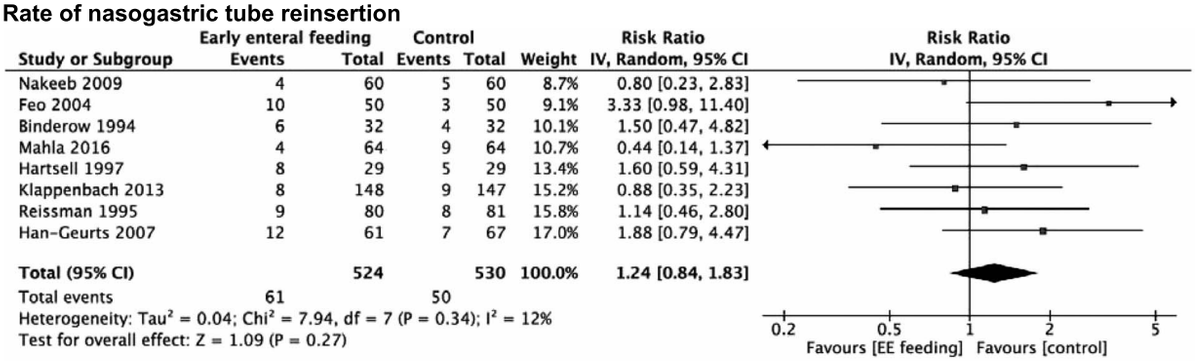
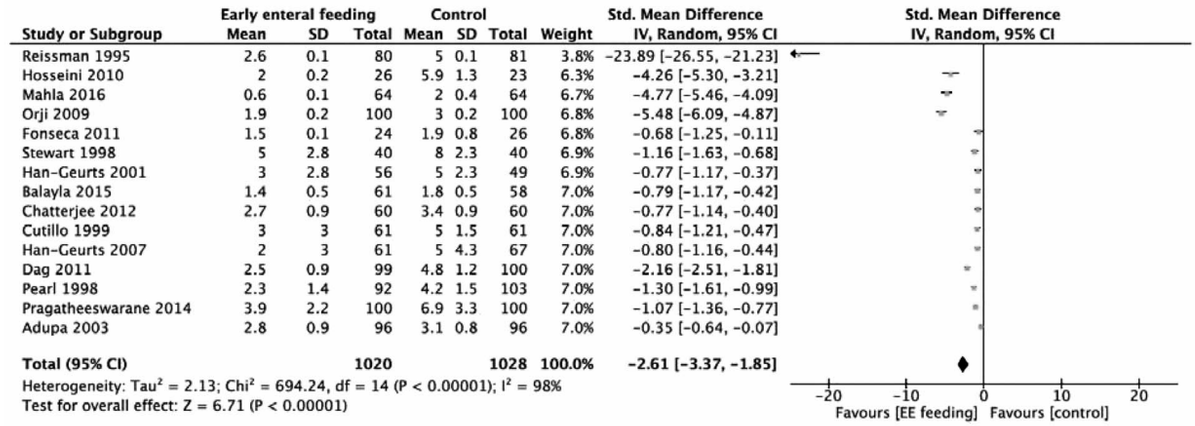
D **Rate of nasogastric tube reinsertion**



E **Attainment to the goal of enteral feeding**



F **Hospital length of stay**

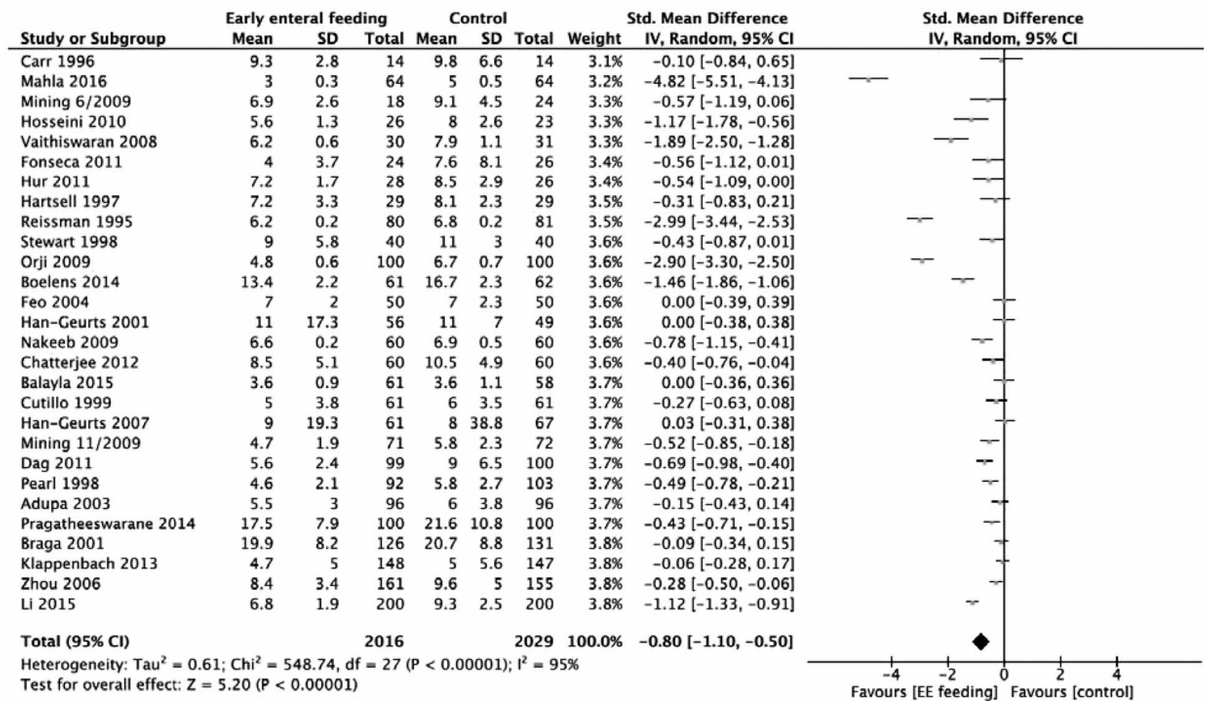


Figure 4. Continued.

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The selected studies included patients who underwent elective gastrointestinal surgeries,[25–33] elective colorectal surgery,[34–47] vascular surgery,[35,43] emergent abdominal surgery,[48] and gynecologic surgery.[49–56] Overall, included studies were heterogeneous in terms of inclusion/exclusion criteria and in the way EEN was delivered (oral diet or tube feeding). In all included studies, EEN was started during the first 24 hours to 48 hours after admission to the hospital or after the surgical procedure. In the control groups, enteral nutrition was started after ileus resolution[25,27–30,32,33,35–56] or parenteral nutrition was started on the same day of the surgery.[26,31,34]

Overall EEN was found to be safe and well tolerated,[25,27–29,32–34,36–41,43–54,56] resulted in faster return of normal bowel function,[25,27,30,34,40,42,47,51] and improved nutritional status.[26,29,32,43] Three studies reported no beneficial effect of EEN on the resolution of ileus.[35,49,53] The overall the rate of adverse effects related to EEN, such as nausea, vomiting, wound infections, anastomotic leaks and pulmonary complications, did not differ between EEN and comparison groups.

QUANTITATIVE ANALYSIS

All studies were included in the meta-analysis. EEN was associated with faster return of normal bowel function, defined as: time to first flatus (SMD, −0.99; 95% CI, −1.40 to −0.58), time to first bowel movement (SMD, −0.91; 95% CI, −1.30 to −0.52), duration of NGT (SMD, −1.09; 95% CI, −1.88 to −0.30), NGT reinsertion rate (RR, 1.24; 95% CI, 0.84–1.83); attainment of enteral feeding goal (SMD, −2.61; 95% CI, −3.37 to −1.85), and hospital LOS (SMD, −0.80; 95% CI, −1.10 to −0.50) (Fig. 4).

GRADING THE EVIDENCE

The evidence was assessed applying the GRADE framework (Table 3). The level of evidence was decreased for imprecision when results were reported with wide confidence intervals in NGT reinsertion rate.

The bias assessment revealed a significant lack of blinding of either the participant or the research staff to the studies' group assignments (performance bias). Also sequence generation and allocation concealment (selection bias) was not clearly described in more than half of the included studies (Supplemental Digital Content 3, Figure 3, http://links.lww.com/TA/B416). Overall the level of evidence for PICO 3 was assessed as low.

RECOMMENDATIONS FOR THE USE OF EEN (PICO 3)

Based on the analysis of included studies, the effect of EEN on the selected outcomes, and the quality of the evidence, we strongly recommend using EEN in adult surgical patients to hasten ileus resolution.

USING THESE GUIDELINES IN CLINICAL PRACTICE

This systematic review evaluated the effects of metoclopramide, erythromycin, and EEN on the resolution of ileus in surgical patients.

TABLE 4. Recommendations

PICO	Recommendation
(1) The use of metoclopramide	We cannot recommend for or against the use of metoclopramide in adult surgical patients to hasten ileus resolution.
(2) The use of erythromycin	We cannot recommend for or against the use of erythromycin in adult surgical patients to hasten ileus resolution.
(3) The use of EEN	We strongly recommend using EEN in adult surgical patients to hasten ileus resolution.

Early enteral nutrition was found to be effective and safe in facilitating resolution of ileus. The included studies defined EEN as enteral nutrition in any dosage that was initiated within 24 hours to 48 hours after the operation. EEN reduced time to return of normal bowel function, and shortened hospital LOS. The adverse events attributed to EEN were minimal and did not affect clinically relevant patient outcomes. Although the level of evidence supporting our conclusion was low, the overwhelming beneficial effect of EEN on the selected outcomes, the large number of included RCT and patients, and the safety of EEN allowed us to make a strong recommendation to use EEN to accelerate resolution of ileus.

The evidence to support usage of metoclopramide or erythromycin in surgical patients was poor. None of the selected outcomes (return of normal bowel function, attainment of enteral feeding goal, and hospital LOS) were positively affected by either metoclopramide or erythromycin. Only a few studies reported complications in either the metoclopramide or erythromycin groups; the incidence of these events was low and did not affect patient outcomes. No metoclopramide-related adverse events were reported. Only a few episodes of skin rash were described in the erythromycin groups. Based on the analysis of included studies, the effect of either metoclopramide or erythromycin on the selected outcomes, and low level of evidence, we could not make recommendations for or against the use of either metoclopramide or erythromycin in surgical patients to hasten the resolution of ileus.

CONCLUSION

For the use of metoclopramide in adult surgical patients to hasten ileus resolution, we cannot recommend for or against. We cannot recommend for or against the use of erythromycin in adult surgical patients to hasten ileus resolution. We strongly recommend using EEN in adult surgical patients to hasten ileus resolution (Table 4).

AUTHORSHIP

N.B. participated in the study design, literature search, data collection, data analysis, data interpretation, drafting the article. B.B. participated in the study design, data collection, data interpretation, and critical revisions. W.C. participated in the study design, data collection, data interpretation, and critical revisions. J.C. participated in the study design, data collection, data interpretation, and critical revisions. M.C. participated in the study design, data collection, data interpretation, and critical revisions. P.F. participated in the study design, data collection, data interpretation, and critical revisions. R.G. participated in the study design, data collection, data interpretation, and critical revisions. S.G. participated in the study design, data

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collection, data interpretation, and critical revisions. G.K. participated in the study design, data collection, data interpretation, and critical revisions. D.K. participated in the study design, data collection, data interpretation, and critical revisions. C.M. participated in the study design, data collection, data interpretation, and critical revisions. B.R. participated in the study design, data collection, data interpretation, and critical revisions. E.S. participated in the study design, data collection, data interpretation, and critical revisions, and D.D.Y. participated in the study idea, study design, literature search, data collection, data analysis, data interpretation, and critical revisions.

DISCLOSURE

The authors declare no conflicts of interest.

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