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Effect of Early vs Late Start of Oral Intake on Anastomotic Leakage Following Elective Lower Intestinal Surgery: A Systematic Review

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Abstract

Background: Experimental and clinical studies have demonstrated a beneficial effect of early enteral nutrition (EN) on anastomotic leakage following colorectal surgery. Early oral intake is a common form of early EN with various clinical benefits, but the effect on anastomotic leakage is unclear. This systematic review investigates the effect of early vs late start of oral intake on anastomotic leakage following lower intestinal surgery. *Methods:* A systematic literature search was performed using the PubMed, Embase, Medline, and Cochrane databases. Randomized controlled trials were included that compared early (within 24 hours) vs late start of oral intake following elective surgery of the small bowel, colon, or rectum. Meta-analysis was performed for anastomotic leakage, overall complications, length of stay, and mortality. Sensitivity analysis was performed in which studies of inferior methodological quality were excluded. *Results:* Nine studies including 879 patients met eligibility criteria. Early start of oral intake significantly reduced overall complications (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.46–0.93; $P = .02$), length of stay (mean difference, −0.89; 95% CI, −1.22 to −0.57; $P < .001$), and anastomotic leakage (OR, 0.40; 95% CI, 0.17–0.95; $P = .04$) compared with late start of oral intake. However, in the sensitivity analysis only the overall reduction of length of stay remained significant. *Conclusion:* The effect of early oral intake on anastomotic leakage is unclear as existing studies are heterogeneous and at risk of bias. High-quality studies are needed to study the potential benefit of EN on anastomotic healing. (*Nutr Clin Pract.* 2018;33:803–812)

Keywords

enteral nutrition; surgery; wound healing; nutritional support; colorectal surgery; anastomotic leak; length of stay; mortality; meta-analysis

Anastomotic leakage (AL) is a severe complication following colorectal surgery as it is associated with increased morbidity, mortality, and cancer recurrence rates.[1-4] Despite ongoing efforts, strategies that effectively reduce AL are lacking and the incidence has remained stable over the years.[5]

Several experimental studies have demonstrated that enteral nutrition (EN) may improve anastomotic healing.[6-12] Moreover, in 2 recent randomized controlled trials, AL following colorectal surgery was significantly reduced by means of early postoperative EN[13] and direct perioperative sham feeding.[14] Taken together, these results suggest that EN administered close to surgery may provide new therapeutic opportunities to reduce AL.

A common method to provide EN close to surgery is the early postoperative start of oral intake. Systematic reviews on the effects of early start of oral intake following gastrointestinal (GI) surgery have demonstrated clear benefits, including a reduction in length of stay (LOS), overall complications, and mortality.[15-18] However, in these reviews, early oral intake did not affect AL.[15-18] Importantly, these systematic reviews included various types of GI surgery or included studies that combined other elements of fast-track protocols in the intervention group but not in the control group.[15-18] To further investigate the potential beneficial effects of EN on anastomotic healing, this systematic review

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compares the effect of early vs late start of oral intake on AL following elective lower intestinal surgery.

Methods

This systematic review was performed according to the Cochrane Handbook for Systematic Reviews for Interventions[19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[20] The entire review process (ie, article search, critical appraisal, data extraction, and analysis) was conducted by 3 independent researchers (B.J.J.S., E.G.P., and E.C.J.H.). Any disagreements were resolved through discussion.

Eligibility Criteria

We included only randomized controlled clinical trials that reported on the effects of early vs late start of oral intake on AL following elective surgery of the small bowel, colon, or rectum in patients aged ≥18 years. We defined early start of oral intake as any caloric intake started within 24 hours after surgery. Late start of oral intake was defined as nil by mouth until resolution of postoperative ileus (ie, passage of flatus or stool without presence of nausea or vomiting). To assess the true effect of early oral intake alone, we excluded studies that combined early oral intake with other elements of fast-track protocols in the intervention group but not in the control group.

Information Sources and Search Strategy

The PubMed, Medline, Embase, and Cochrane databases were systematically searched. The search strategy combined all synonyms regarding the intervention "early oral intake" and the domain "lower intestinal surgery" with the Boolean operator "AND." All synonyms were combined with the Boolean operator "OR." An example set of search terms is provided in Supplementary Table S1. We tested the sensitivity of the search strategy by screening all references of included articles for relevant publications that were not retrieved in the initial search. Furthermore, we screened all citing articles and related articles using Web of Science version 5.15.1. Identification of additional eligible articles led to evaluation and improvement of the search strategy until it retrieved all eligible articles. We contacted authors by email if articles were not available in full text. The search was updated until September 28, 2016.

Study Selection

Three authors screened all records on title and abstract. Records were excluded if they clearly did not address the domain and intervention under investigation. The remaining articles were screened in full text. Only articles fulfilling all eligibility criteria were included.

Data Extraction and Outcomes

The relevant published data were collected in pilot-tested tables. Extracted information from each study included (1) study information, including name of first author, year of publication, number of participants in each group, and reported outcomes; (2) patient information, including type of surgery, disease, sex, age, and perioperative protocols used affecting AL[21]; and (3) postoperative feeding protocols. Furthermore, we extracted data on the incidence and definition of AL, overall complications, mortality, and LOS.

Risk of Bias in Individual Studies

All studies included in the review were investigated for risk of bias with the Cochrane collaboration's tool for assessing risk of bias.[19] Risk of bias was assessed on the following items: randomization method, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and any other item in study design.

Data Analysis

Meta-analysis was performed for AL, overall complications, LOS, and mortality. We performed data analysis using Review Manager Software version 5.3 as recommended by the Cochrane Handbook for Systematic Reviews for Interventions.[19,22] Dichotomous results were analyzed using the random-effects model in the Mantel-Haenszel method and are presented as odds ratio (ORs) with corresponding 95% confidence intervals (CIs). Continuous results were analyzed using the inverse variance method and are presented as mean difference (MD) with corresponding 95% CI. A P value $<.05$ was considered to be statistically significant. We assessed presence and amount of statistical heterogeneity using the I^2 statistic. Furthermore, a sensitivity analysis was performed in which studies of inferior methodological quality were excluded.

Results

Description of Studies

Figure 1 presents the search results and study selection process. The search revealed 80 potentially relevant studies, of which 9 randomized controlled trials fitted inclusion criteria. Study characteristics are shown in Table 1. Types of surgical procedures were evenly matched between groups in all studies. Laparoscopic surgery was performed only in 1 study[23]; in other studies, open surgery was performed.[24-31] When reported, there was substantial heterogeneity between studies in the use of perioperative protocols, including use of epidural anesthesia, preoperative bowel lavage, nonsteroid anti-inflammatory drugs, and

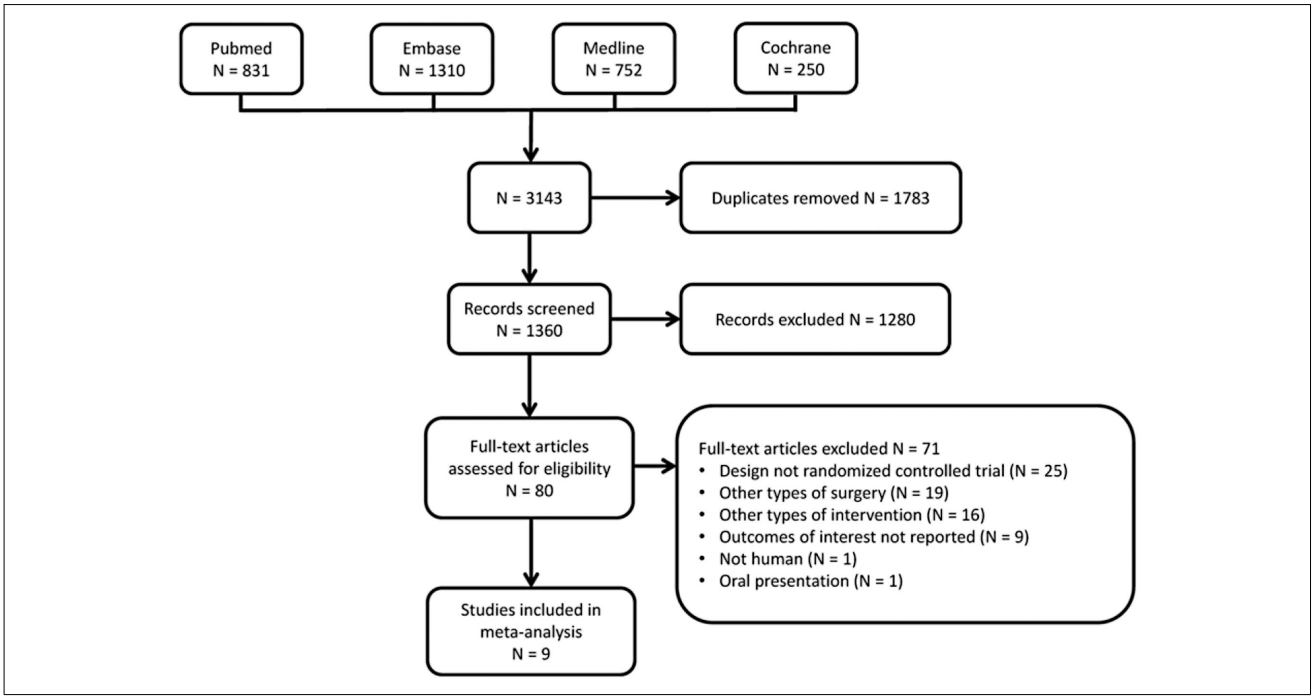

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for search results and study selection process.

opioids. Postoperative feeding protocols are described in Table 2.

AL was a rare event in most studies and rarely a primary outcome. Four studies provided definitions for AL (Table 3).[25,26,28,31]

Methodological Quality of Included Studies

Due to the nature of the intervention, blinding could not be applied in any study. Three studies gave no explicit description of the randomization method, resulting in an unclear risk of bias.[26,27,30] One open-label study used blocked randomization with a fixed block size of 6; hence, risk of selection bias was present.[29] In the same study, it was unclear whether the nasogastric tube was postoperatively removed in both groups at similar time points. In 1 study,[28] patients allocated to delayed start of oral intake had a significantly greater amount of intraoperative blood loss (early oral intake median 300 mL vs delayed oral intake median 800 mL, $P = .002$), which is a known risk factor for AL.[21] The summary of risk of bias assessment is shown in Table 4. Overall, 3 studies were identified to have the best available methodological quality and were entered in the sensitivity analysis.[23,24,31]

AL

First, all studies were entered in the meta-analysis regardless of methodological quality. As shown in Figure 2A, early start of oral intake significantly reduced AL compared with late start of oral intake (OR, 0.40; 95% CI, 0.17–0.95; $P = .04$). However, when trials with risk of bias were excluded in the sensitivity analysis, the overall effect on AL was no longer significant (OR, 0.39; 95% CI, 0.09–1.76; $P = .22$) (Figure 2B).

Overall Complications

All studies provided data on overall complications. As shown in Figure 3A, early start of oral intake significantly reduced overall complications compared with late start of oral intake (OR, 0.65; 95% CI, 0.46–0.93; $P = .02$). However, when trials with risk of bias were excluded in the sensitivity analysis, the overall effect on overall complications was no longer significant (OR, 0.74; 95% CI, 0.42–1.31; $P = .30$) (Figure 3B).

LOS

Seven studies provided data on LOS as mean ± standard deviation and were entered in the meta-analysis.[23-26,28-30] As shown in Figure 4A, early start of oral intake significantly reduced LOS compared with late start of oral intake (MD, −0.89; 95% CI, −1.22 to −0.57; $P < .001$). Excluding studies with risk of bias increased the overall effect of LOS (MD, −3.47; 95% CI, −4.73 to −2.21; $P < .001$) (Figure 4B).

Table 1. Study Characteristics.[a]

Author and Publication Year	Site of Surgery	Disease	Mean Age, y		Sex (Male/Female), No.		Reported Postoperative Outcomes
			Early Oral Intake	Late Oral Intake	Early Oral Intake	Late Oral Intake	
da Fonseca et al,[23] 2011	Colon	NR	57	52	8/16	10/16	LOS, recovery of GI function, overall morbidity, anastomotic leakage, readmission, surgical reintervention after discharge, mortality
Dag et al,[24] 2011	Colon, rectum	Neoplasia	62	61	52/47	61/39	LOS, recovery of GI function, complications
El Nakeeb et al,[25] 2009	Colon, rectum	Neoplasia	52	56	39/21	42/18	LOS, recovery of GI function, complications, readmission, mortality
Hartsell et al,[26] 1997	Colon, rectum	Neoplasia, diverticular disease, inflammatory bowel disease	66	68	NR	NR	LOS, recovery of GI function, complications
Lucha et al,[27] 2005	Colon, rectum	NR	51	51	17/9	16/9	LOS, recovery of GI function, aspiration pneumonia, anastomotic leakage, antiemetic medication, admission costs
Minig et al,[28] 2009	Small bowel, colon, rectum	Gynecological neoplasia	54	58	0/18	0/22	LOS, recovery of GI function, complications, intensity of abdominal pain, patient satisfaction level, quality of life, antiemetic and analgesic medication
Pragatheeswarane et al,[29] 2014	Small bowel, colon, rectum	Neoplasia, familial adenomatous polyposis, stricture	47	47	33/27	32/28	LOS, recovery of GI function, complications
Reissman et al,[30] 1995	Small bowel, colon, rectum	NR	51	56	34/46	43/38	LOS, recovery of GI function, complications
Stewart et al,[31] 1998	Colon, rectum	NR	58	59	19/21	18/22	LOS, recovery of GI function, complications, antiemetic and analgesic medication, mobilization

GI, gastrointestinal; LOS, length of stay; NR, not reported.
[a] All values are presented as patient numbers unless indicated otherwise.

Table 2. Postoperative Feeding Protocols.

Author and Publication Year	Early Oral Intake	Late Oral Intake
da Fonseca et al,[23] 2011	POD1 oral liquid diet, advance to regular diet within 24 hours as tolerated	SC
Dag et al,[24] 2011	12 hours postoperatively, start fluids, advance to solid diet as tolerated	SC
El Nakeeb et al,[25] 2009	POD1 fluids, advance to regular diet within 24–48 hours as tolerated	SC
Hartsell et al,[26] 1997	POD1 full liquid diet, advance to regular diet if >1000 mL was consumed within 24 hours	SC
Lucha et al,[27] 2005	8 hours after surgery, start regular diet	SC
Minig et al,[28] 2009	POD0 CL, advance to regular diet on POD1 as tolerated	SC
Pragatheeswarane et al,[29] 2014	POD1 CL, advance to full fluid diet within 48 hours, start solid diet over next 24 hours	SC
Reissman et al,[30] 1995	POD1 CL, advance to regular diet as tolerated	SC
Stewart et al,[31] 1998	4 hours postoperatively, start free fluids, advance to solid diet as tolerated on POD1	SC

CL, clear liquids; POD, postoperative day; SC, standard care (nil by mouth until resolution of ileus).

Table 3. Definitions for Anastomotic Leakage.

Author and Publication Year	Definition
El Nakeeb et al,[25] 2009	Symptoms such as fever and leakage of intestinal contents
Hartsell et al,[26] 1997	Resulting in sepsis and eventual death
Minig et al,[28] 2009	Requiring surgical reexploration
Stewart et al,[31] 1998	Fecal discharge from drain tube, which settled without intervention

Mortality

Seven studies provided data on mortality and were entered in the meta-analysis.[23,25,26,28-31] As shown in Figure 5A, early start of oral intake did not affect mortality compared with late start of oral intake (OR, 0.61; 95% CI, 0.17–2.22; $P = .45$). Excluding studies with risk of bias did not alter the overall effect of early start of oral intake on mortality (OR, 1.04; 95% CI, 0.10–10.35; $P = .97$) (Figure 5B).

Discussion

The current review demonstrates that the effect of early oral intake on AL is unclear in a clinical setting. This is mainly due to a lack of high-quality evidence, since existing randomized trials are clinically heterogeneous and at risk of bias.

Experimental studies have suggested that EN can improve anastomotic healing via several mechanisms.[6-12] These experimental findings may be corroborated by 2 randomized clinical trials of good methodological quality that demonstrated a reduction of AL by means of perioperative sham feeding[14] (ie, gum-chewing) and early postoperative enteral tube feeding.[13] Early start of oral intake is a more common form of early EN and has been extensively described as part of fast-track protocols in colorectal surgery. Individual randomized trials have described no effect of early oral intake on AL, but most studies had a relatively small sample size and were therefore inadequately powered to detect a potential effect on AL.[23-31] Previous systematic reviews on early EN also did not support an effect on AL.[15-18] However, these reviews may have been inadequate to assess the true effect of EN, since they included studies with patients undergoing upper GI surgery,[32] studies that applied immunonutrition,[33] or studies that applied other aspects of fast-track protocols only in the treatment group but not in the control group (eg, early nasogastric tube removal).[34] Furthermore, no review performed a sensitivity analysis to minimize the risk of bias.[15-18] This study therefore aimed to provide an update of the available literature and to perform a rigorous critical appraisal and sensitivity analysis to examine the true effect of EN on anastomotic healing in a clinical setting. In the current meta-analysis, the pooling of all 9 randomized trials regardless of methodological quality resulted in several beneficial effects in favor of early oral intake. However, the strict exclusion of 6 studies with a modest to high risk of bias[25-30] in the sensitivity analysis significantly reduced overall sample size and made the effect on AL and overall complications no longer significant. As such, the results from our study suggest that early start of oral intake is only associated with a reduction of length of stay (LOS).

The overall reduction of LOS following early oral intake ranges from almost 1 day in the general meta-analysis to approximately 3 days in the sensitivity analysis. This may be explained by a faster return of bowel function in the early feeding group, as demonstrated by various indicators

Table 4. Critical Appraisal of Included Studies.

Item	da Fonseca et al,[23] 2011	Dag et al,[24] 2011	El Nakeeb et al,[25] 2009	Hartsell et al,[26] 1997	Lucha et al,[27] 2005	Minig et al,[28] 2009	Pragatheeswarane et al,[29] 2014	Reissman et al,[30] 1995	Stewart et al,[31] 1998
Randomization?	+	+	+	?	?	+	+	?	+
Allocation concealment?	+	+	?	?	?	+	−	?	+
Blinding of participants and personnel?	−	−	−	−	−	−	−	−	−
Blinding of outcome assessment?	−	−	−	−	−	−	−	−	−
Complete outcome data?	+	+	+	+	+	+	+	+	+
No selective reporting?	+	+	+	+	+	+	+	+	+
No other bias?	+	+	+	+	+	−	?	+	+

+, yes; –, no; ?, unclear.

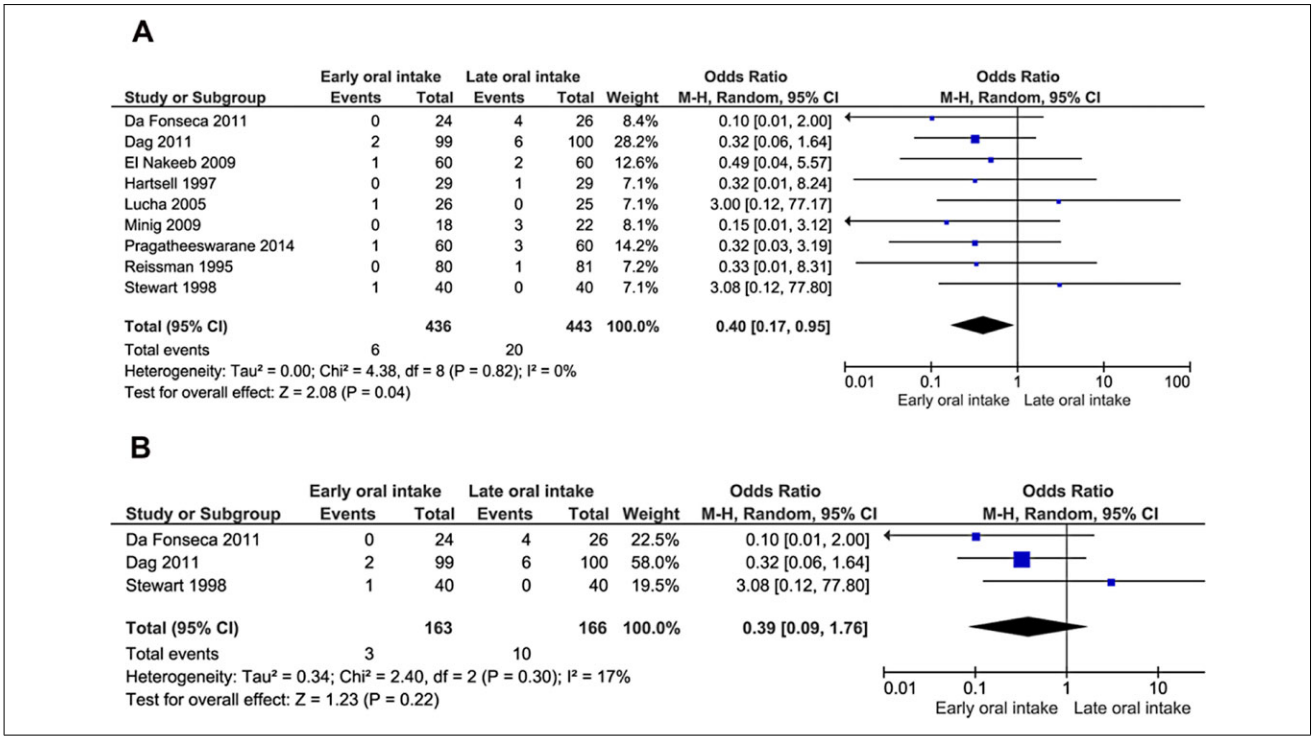

Figure 2. (A) Forest plot for studies that examined the effect of early vs late start of oral intake for anastomotic leakage. (B) Sensitivity analysis for studies that examined the effect of early vs late start of oral intake for anastomotic leakage. M-H, Mantel-Haenszel.

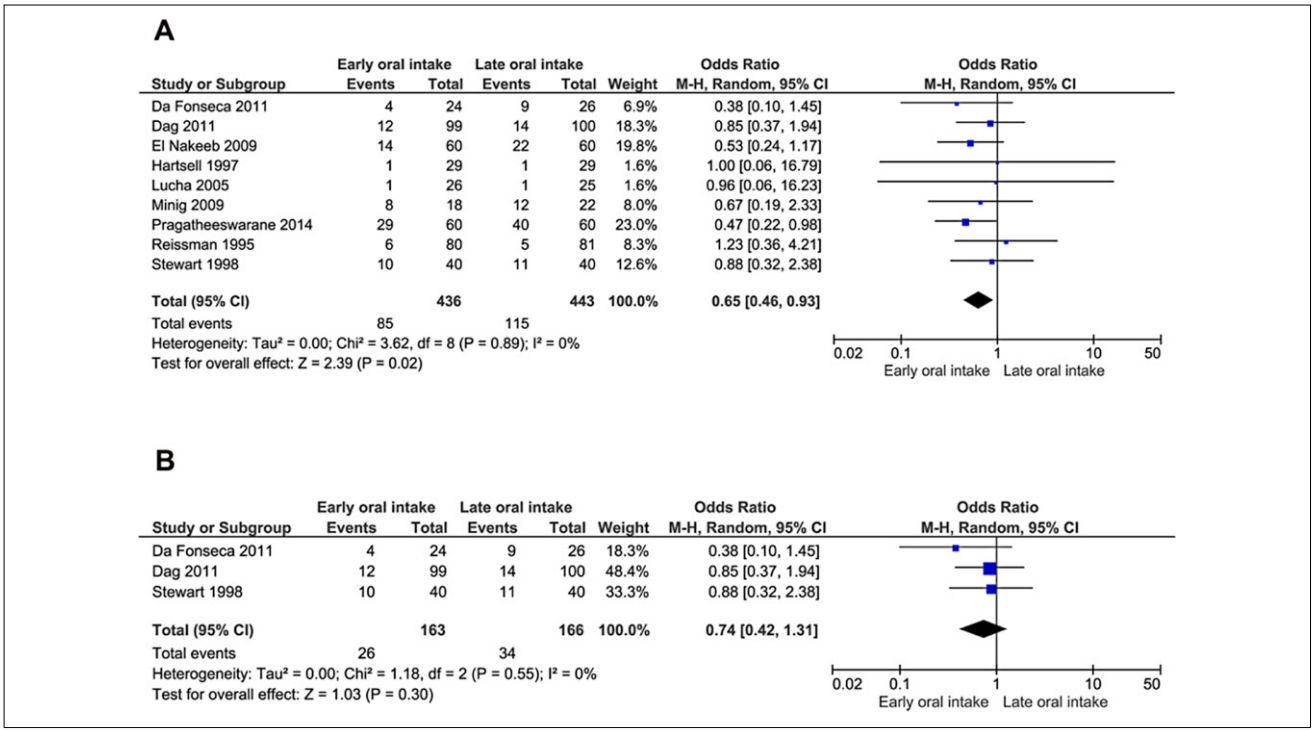

Figure 3. (A) Forest plot for studies that examined the effect of early vs late start of oral intake for overall complications. (B) Sensitivity analysis for studies that examined the effect of early vs late start of oral intake for overall complications. M-H, Mantel-Haenszel.

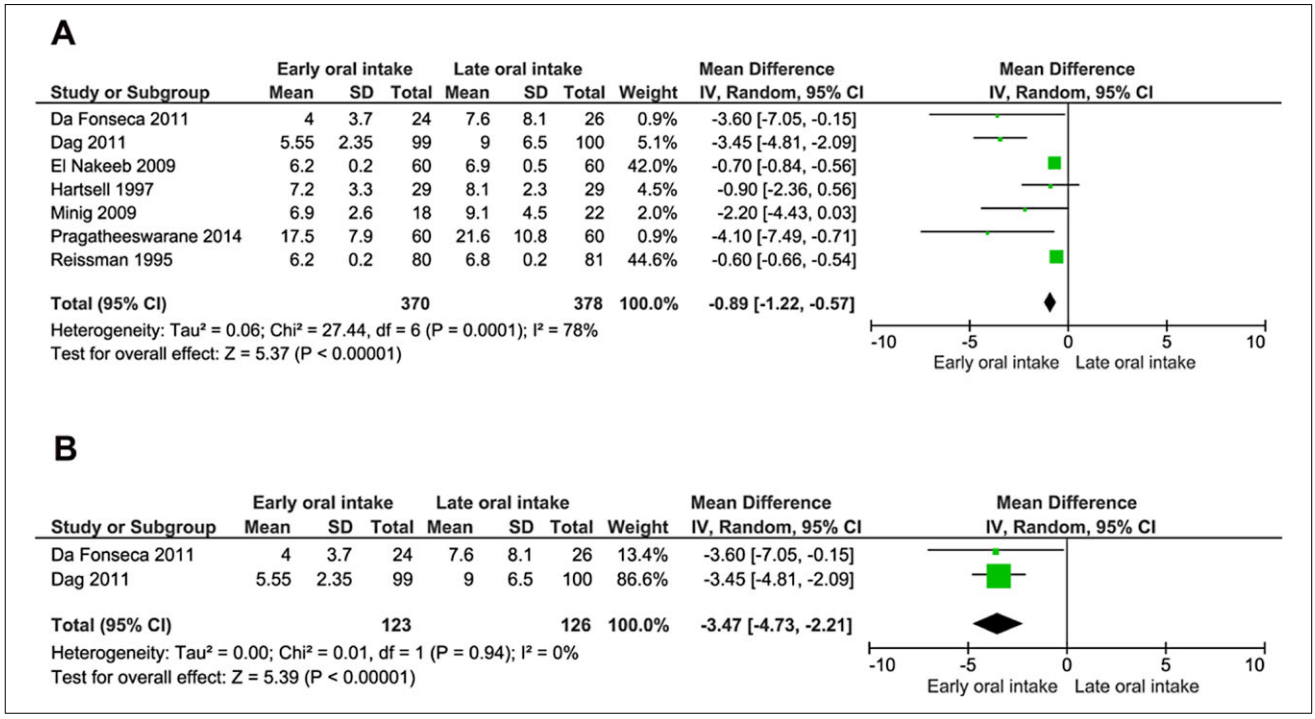

Figure 4. (A) Forest plot for studies that examined the effect of early vs late start of oral intake for length of stay. (B) Sensitivity analysis for studies that examined the effect of early vs late start of oral intake for length of stay. IV, inverse variance; M-H, Mantel-Haenszel.

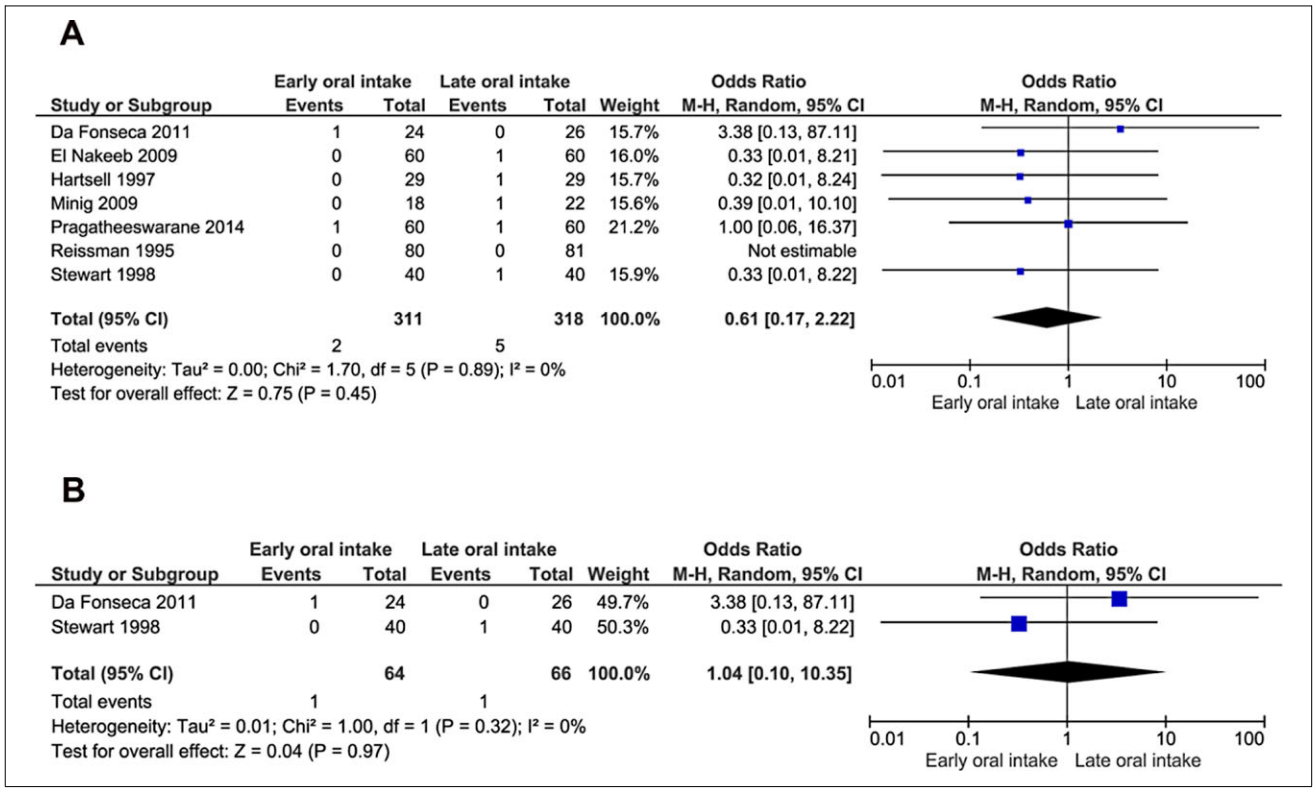

Figure 5. (A) Forest plot for studies that examined the effect of early vs late start of oral intake for mortality. (B) Sensitivity analysis for studies that examined the effect of early vs late start of oral intake for mortality. M-H, Mantel-Haenszel.

of GI motility (eg, time to first flatus or defecation) in multiple studies.[23-25,29] However, differences in discharge criteria between the included studies may have confounded the effect of early oral intake on LOS, as suggested by the high statistical heterogeneity.

Despite the attempt to minimize risk of bias by means of a sensitivity analysis, several other limitations remain present in the current systematic review. First, perioperative protocols varied greatly between studies, including the use of nonsteroid anti-inflammatory drugs and preoperative bowel lavage. However, while differences in these protocols can affect various clinical outcomes, the specific effect on AL may be limited except for nonsteroid anti-inflammatory drugs.[21] Second, no study was blinded; however blinding is difficult to apply due to the nature of the intervention. Third, the included studies involved various sites of lower intestinal surgery; it is well known that the a priori risks of AL vary in the small bowel, colon, and rectum. However, in the sensitivity analysis, only studies including colorectal surgery were included. Last, a clear definition for AL lacked in most studies and varied between studies when provided. While this review attempts to summarize best available evidence, the generalizability remains limited by the heterogeneity of the included studies.

In conclusion, the results of this systematic review suggest that early oral intake is associated with a reduction in LOS, while the effect on anastomotic healing remains unclear as existing literature is clinically heterogeneous and at risk of bias. More well-designed, high-quality randomized studies are needed to further study the potential benefit of EN, since alternative strategies that reduce AL are lacking.

Statement of Authorship

B. J. J. Smeets and M. D. P. Luyer equally contributed to the conception and design of the research; T. J. Weijs contributed to the design of the research; and B. J. J. Smeets, E. G. Peters, and E. C. J. Horsten contributed to the acquisition and analysis of the data and drafted the manuscript. All authors contributed to the interpretation of the data, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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