Effect of early enteral nutrition on patients with digestive tract surgery: A meta-analysis of randomized controlled trials

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Abstract. Postoperative early enteral nutrition (EEN) is useful for the effective recovery of patients that have undergone surgery. However, the feasibility and efficacy of EEN in patients with digestive tract surgery remain inconclusive. In the present meta-analysis, the PubMed, EMBASE, Web of Science, The Cochrane Library, China National Knowledge Infrastructure and VIP databases were searched to identify controlled trials of patients with and without EEN following digestive tract surgery between October, 1966 and December, 2014. Methodological quality assessment was carried out for each of the included studies. For estimation of the analysis indexes, relative risk (RR) was used as the effect size of the the categorical variable, while the weighted mean difference (MD) was used as the effect size of the continuous variable. The meta-analysis was conducted using RevMan 5.2 software. Eleven randomized controlled trials involving 1,095 patients were included in the meta-analysis. The results revealed that, EEN in patients with digestive tract surgery was more effective in decreasing the incidence of infectious [RR=0.50, 95% confidence interval (CI): 0.38, 0.67; P<0.01] and non-infectious complications (RR=0.72, 95% CI: 0.43, 1.22; P<0.05) and shortening the length of first bowel action (MD=-4.10, 95% CI: -5.38, -2.82; P<0.05). It also had a significant influence on increasing the serum albumin (MD=2.87, 95% CI: 1.03, 4.71; P<0.05) and serum prealbumin (MD=0.04, 95% CI: 0.02, 0.05; P<0.05) levels. In conclusion, the results of the study have shown that EEN in patients with digestive tract surgery improved the nutritional status, reduced the risk of postoperative complications, shortened the length of hospital stay and promoted the functional recovery of the digestive system.

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Introduction

Parenteral nutrition (PN) and enteral nutrition (EN) are two important supportive therapies for clinical surgical treatment. Early EN (EEN) should be preferred to total PN (TPN) whenever possible or at any point that the patient has a functioning gut (1-4).

Numerous studies showed that EEN had a positive influence on improving intestinal function and reducing the incidence of postoperative complications, especially for severe illness (5-7). Additionally, EEN has been demonstrated to be more physiological, to prevent morphologic and functional trauma-related alterations of the gut, to modulate the immune and inflammatory responses to injury, and to be more cost-efficient than TPN (8-12). However, the feasibility and efficacy of EEN in patients with digestive tract surgery has remained inconclusive.

Randomized controlled trials (RCTs) (13) suggested that the early resumption of oral intake does not decrease the duration of postoperative ileus or lead to a significantly increased rate of nasogastric tube reinsertion. Eckerwall *et al* found that the overall early complication rate was higher in EN than TPN in patients with predicted severe acute pancreatitis (14).

The present meta-analysis was performed to investigate RCTs in patients with and without EEN after digestive tract surgery to provide concrete clinical evidence for the feasibility and efficacy of EEN.

Materials and methods

Study selection. The databases PubMed (http://www.pubmed.com), EMBASE (http://www.embase.com), Web of Science (http://apps.webofknowledge.com), The Cochrane Library (http://www.thecochranelibrary.com), China National Knowledge Infrastructure (CNKI; http://www.cnki.net/) and VIP (http://www.cqvip.com/) were systematically searched for RCTs concerning the effect of EEN (using the key terms: 'early feeding', 'early postoperative feeding', 'early postoperative enteral nutrition', 'early postoperation oral feeding', 'immediate enteral nutrition', 'immediate postoperative feeding' and their variants) in patients with digestive tract surgery (using the key terms 'operation', 'gastrointestinal surgery', 'upper digestive tract', 'alimentary tract', 'gut', 'colorectal', 'colon', 'rectum', 'stomach', 'pancreas', 'duodenum', 'gastric', 'intestinal', 'gastrectomy', and 'enterectomy' and their variants). When multiple articles for a similar study were found, we considered only the most complete and recently published ones and supplemented the present meta-analysis, if necessary, with data from the most complete or updated publication. References from the extracted articles and reviews were also consulted to complete the data bank.

Studies were included for the present meta-analysis if they complied with the following inclusion criteria: i) RCTs with parallel controlled design; ii) patients underwent digestive tract surgery for reasons other than renal, cardiac or hepatic failure; iii) EEN was provided within one postoperative day in the treatment group; iv) biochemical indices (serum total protein, serum albumin and serum prealbumin), length of first bowel action, infectious and non-infectious complications and length of hospital stay; and v) supplementary data relevant to this meta-analysis were available. Studies were excluded from the present meta-analysis due to: i) patients not being randomized; ii) inadequate statistical analysis; and iii) use of animal trials, less relevant, review articles and case reports.

Data extraction. From each study, we extracted information regarding first author, year of publication, country of origin, sample size, age, gender, type of diseases or surgeries, average study follow-up time, type of intervention, duration of intervention, disease outcome, method of outcome ascertainment, unit of measurement and corresponding 95% confidence intervals (CIs), standard error (SEs), or exact P-values from text, and Tables and Figs. Since the differences in the study populations and study design of the included studies potentially cause variations in the results, a study-quality score was calculated using methodological quality assessment (15) for each of the included traits ranging from 0 to 5. Based on this, the studies were categorized into high quality score (3-5 points), low quality score (1-2 points) and no RCTs (0 point).

Data analysis. The data pooling was performed following classical meta-analysis method using the Review Manager (RevMan) (Computer Program). (Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2014; http://ims.cochrane.org/revman/). $P<0.05$ was considered statistically significant. The missing standard deviation (SD) value for one trial was imputed from SD values of the remaining trials using the same measure (16). For estimation of the analysis indexes, relative risk (RR) was used as the effect size of the categorical variable, while the weighted mean difference (MD) was used as the effect size of the continuous variable. The 95% CI was calculated for each investigation and for each outcome variable. The statistical heterogeneity test was performed using the I^2 statistic ($\alpha=0.05$), which assessed the appropriateness of pooling the individual study results prior to calculating the standardized mean effect for all the trials. The I^2 value provided an estimate of the amount of variance across studies because of heterogeneity rather than chance (17). The I^2 values 25, 50 and 75% corresponded to low, moderate and high levels of heterogeneity, respectively. If $P\geq0.05$, the heterogeneity was not substantial and low between the trials. Thus, fixed-effects models were used with the Mantel-Haenszel (M-H) method weighting for combined statistics. If $P<0.05$, the heterogeneity was considered substantial and high between the trials. Consequently, combined results were conducted using the random-effects models, which were inverse variance weighting or the DerSimonian-Laird method based on the fixed-effects models. A priori potential sources of heterogeneity were a concern for publication bias. The possible publication bias was investigated by drawing a funnel plot to search for funnel plot asymmetry and meta-regression based on study size (18).

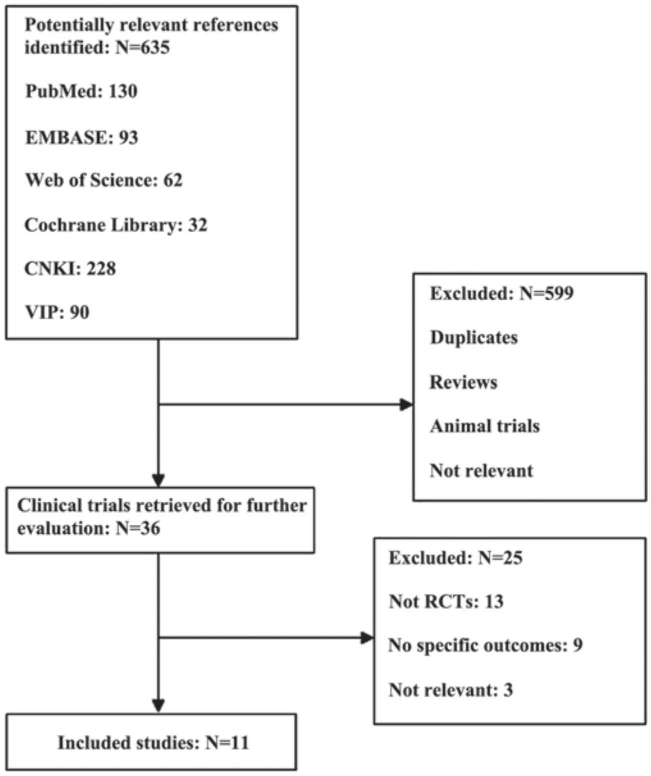

Figure 1. Flow chart showing the trial selection process for this study. RCT, randomized controlled trial; CNKI, China National Knowledge Infrastructure.

Results

Characteristics of the studies. The initial search yielded 635 potentially relevant results and from these only 11 (19,29) RCTs complied with the inclusion criteria and were subsequently included in the present meta-analysis (Fig. 1). A total of 1,095 samples were considered from these 11 RCTs and the sample size varied between studies ranging from 28 to 317. Only the subjects who received EEN within one postoperative day constituted the treatment group for this meta-analysis. The information extracted from these RCTs is presented in Table I. The 11 RCTs were published during the period between October, 1966 to December, 2014.

Relevant biochemical indices

Serum total protein. In total, 126 participants from 3 (24,26,28) of the 11 studies were enrolled to evaluate the change of serum total protein (g/l). Since the heterogeneity of serum between

Table I. Characteristics of the trials included in the present meta-analysis in chronological order by year of publication.

Author (year)	Country	Type of diseases or surgeries	Age, year (treatment/control)	Gender (M/F)	No. of subjects (treatment/control)	Intervention (treatment/control)		Duration, day	Design	Study-quality score	(Refs.)
Schroeder *et al* (1991)	New Zealand	Bowel resection	51±18/ 53±22	17/15	32 (16/16)	POD 1 EN	Routine postoperative feeding	14	DB, C, R	5	(19)
Reissman *et al* (1995)	USA	Elective colorectal surgery	16-90	77/84	161 (80/81)	POD 1 EN	Regular feeding	-	PC, R	3	(20)
Ortiz *et al* (1996)	Spain	Elective colorectal and rectal surgery	22-90	-	190 (91/91)	POD1 EN	Routine postoperative feeding	10	PC, R	3	(21)
Braga *et al* (1996)	Italy	Gastric or pancreatic cancer	59±9/61±7	-	40 (20/20)	POD 1 EN	TPN	7	PC, R	3	(22)
Singh *et al* (1998)	India	Non-traumatic intestinal perforation and peritonitis	38.9±2.1/ 40.8±2.3	-	43 (21/22)	POD 0.5 EN	TPN	7	PC, R	3	(23)
Watters *et al* (1997)	Canada	Esophagectomy or pancreatoduodenectomy	64±11/61±12	22/6	28 (13/15)	POD 1 EN	Unfed	6	PC, R	3	(24)
Stewart *et al* (1998)	Australia	Elective intraperitoneal colorectal resections	17-89	43/37	80 (40/40)	POD 1 EN	POD1-2 EN	10	PC, R	3	(25)
Hu *et al* (1999)	China	Gastrointestinal surgery	38±10.2/ 45±9.8	30/8	38 (18/20)	POD 1 EN	PN	5	PC, R	3	(26)
Bozzetti *et al* (2001)	Italy	Gastrointestinal cancer	64.8±10.8/ 64.1±9.8	185/132	317 (159/158)	POD 1 EN	PN	7	PC, R	3	(27)
Farreras *et al* (2005)	Spain	Gastric cancer	66.7±8.3/ 69.2±13.8	32/28	60 (30/30)	POD 1 EN	Routine postoperative feeding	7	DB, C, R	5	(28)
Wu *et al* (2006)	China	Esophageal carcinoma	33-79	78/28	106 (53/53)	POD 1 EN	PN	7	PC, R	3	(29)

POD, postoperative day; EN, enteral nutrition; PN, parenteral nutrition; TPN, total parenteral nutrition; DB, double-blind; C, control; PC, parallel-controlled; R, randomized.

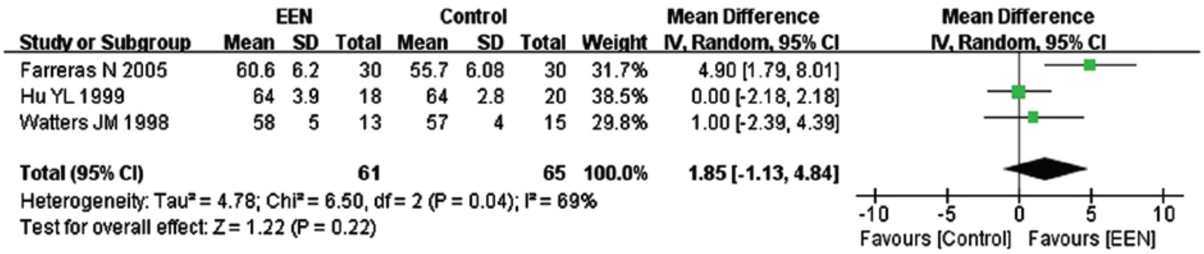

Figure 2. Serum total protein level in treatment [early enteral nutrition (EEN)] and control groups using the random-effects model. SD, standard deviation; CI, confidence interval.

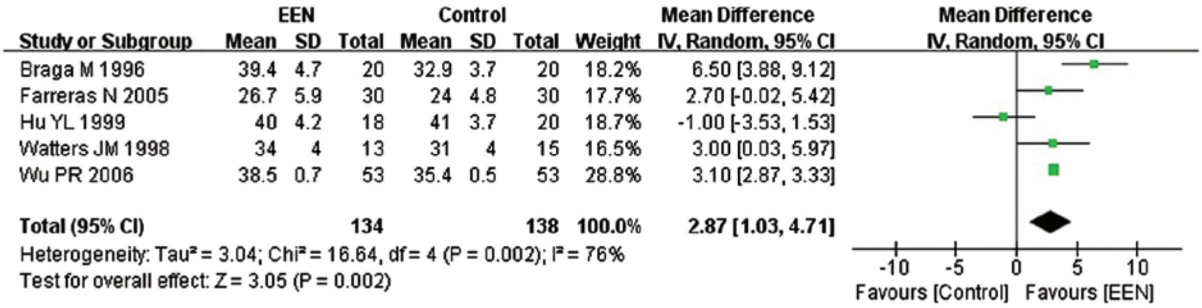

Figure 3. Forest plot of serum albumin level in the treatment [early enteral nutrition (EEN)] and control groups using the random-effects model. SD, standard deviation; CI, confidence interval.

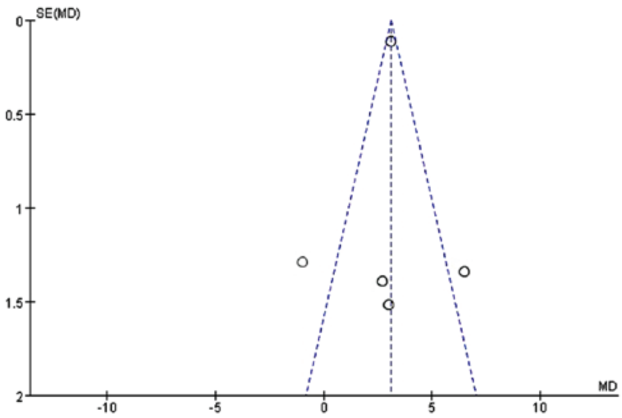

Figure 4. Funnel plot showing the change of serum albumin between the treatment (early enteral nutrition) and control groups. Dotted lines are pseudo 95% confidence intervals. SE, standard error; MD, mean difference.

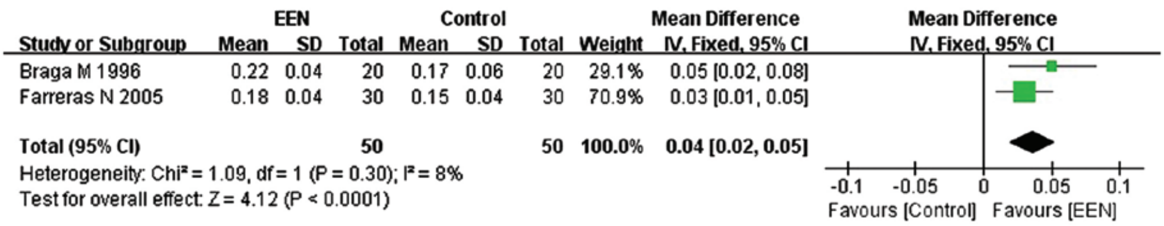

Figure 5. Forest plot of the change of serum albumin level between the treatment [early enteral nutrition (EEN)] and control groups using the fixed-effects model. M-H, Mantel-Haenszel test; SD, standard deviation; CI, confidence interval.

the studies was significant (I^2=69%; P<0.05; χ^2=6.50) the random-effects model was used. From the analysis, we found statistically insignificant difference between the EEN and control group (MD=1.85, 95% CI: -1.13, 4.84; P>0.05) (Fig. 2).

Serum albumin. Approximately 272 participants from 5 of the 11 studies (22,24,26,28,29) were enrolled to evaluate the serum albumin (g/l). Since, the heterogeneity of serum albumin between the studies was significant (I^2=76%; P<0.05;

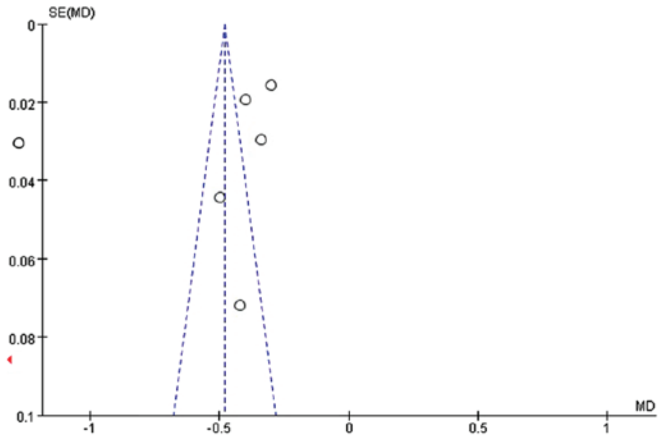

Figure 6. Funnel plot of studies showing the length of first bowel action in treatment (EEN) group and control group. Dotted lines are pseudo 95% confidence intervals. SE, standard error; MD, mean difference.

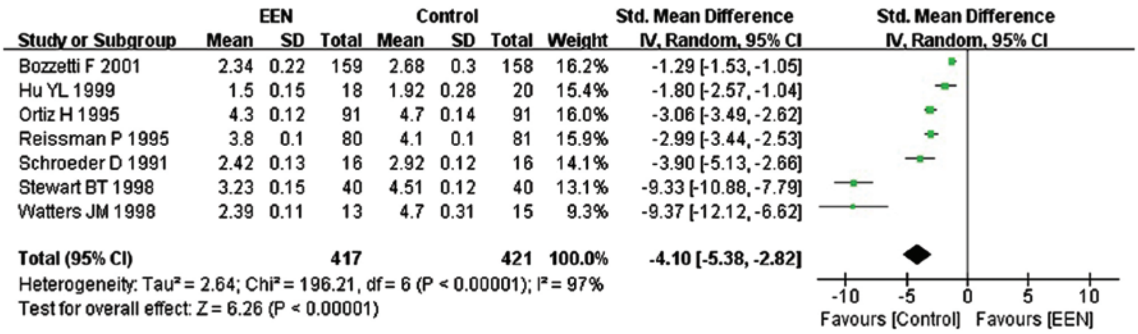

Figure 7. Forest plot showing change of length of first bowel action between treatment [early enteral nutrition (EEN)] group and control group: Random-effects model. SD, standard deviation; CI, confidence interval.

χ^2=16.64) we applied the random-effects model. We found a statistically significant difference between the EEN and control groups (MD=2.87, 95% CI: 1.03, 4.71; P<0.05) (Fig. 3). The symmetry funnel plot suggested scarcely any publication bias existed between studies mentioning change of serum albumin (Fig. 4).

Serum prealbumin. Of the 11 studies, only 2 (22,28) studies with a sample size of 100 subjects focused on serum prealbumin (g/l). The fixed-effects model was used for the heterogeneity to be considered acceptable (I^2= 8%; P>0.05; χ^2=1.09). Our analysis revealed that providing EEN was more effective in increasing the serum prealbumin (MD=0.04, 95% CI: 0.02, 0.05; P<0.05) than the control (Fig. 5).

Length of first bowel action. Information was obtained on the length of first bowel action in 838 patients from 7 studies (19-21,24-27). Since the heterogeneity was significant (I^2= 97%; P<0.05; χ^2=196.21) (Fig. 7) and the asymmetry funnel plot suggested possible publication bias existed between these (Fig. 6), we applied the random-effects model to analyze the data. Our analysis revealed that the patients in the EEN group had a shorter length of first bowel action than the control group (MD=-4.10, 95% CI: -5.38, -2.82; P<0.05) (Fig. 7).

Complications. In 8 studies (19-21,23,25,27-29) analysed, it was found that EEN had an impact on postoperative complications (infectious and non-infectious complications) (Table II) in 981 patients with digestive tract surgery.

Table II. Classification of complications in the included trials.

Sl., no.	Infectious complications	Non-infectious complications
1	Bacteraemia	Anastomotic leak
2	Intra-abdominal abscess	Gastrointestinal bleeding
3	Pelvic abscess	Hemoperitoneum
4	Pneumonia	Hepatic dysfunction
5	Sepsis	Ileus/intestinal obstruction
6	Septic shock	Myocardial infarction
7	Septic coagulopathy	Pancreatic fistula
8	Urinary tract infections	Pancreatitis
9	Wound infections	Pericarditis
10		Pleural effusion
11		Suture failure
12		Renal failure
13		Respiratory failure
14		Venous thrombosis
15		Wound dehiscence

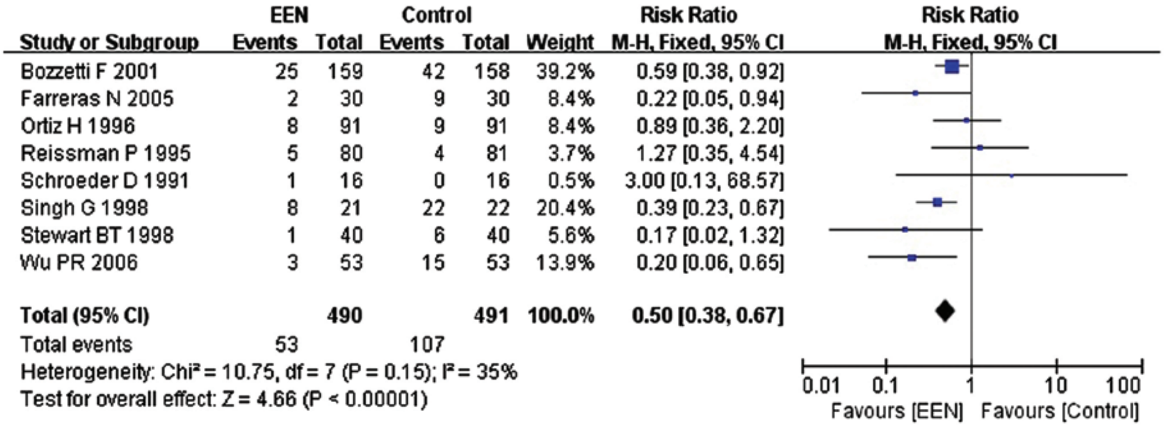

Figure 8. Forest plot of the infectious complications between the treatment [early enteral nutrition (EEN)] and control groups using the fixed-effects model. M-H, Mantel-Haenszel test; SD, standard deviation; CI, confidence interval.

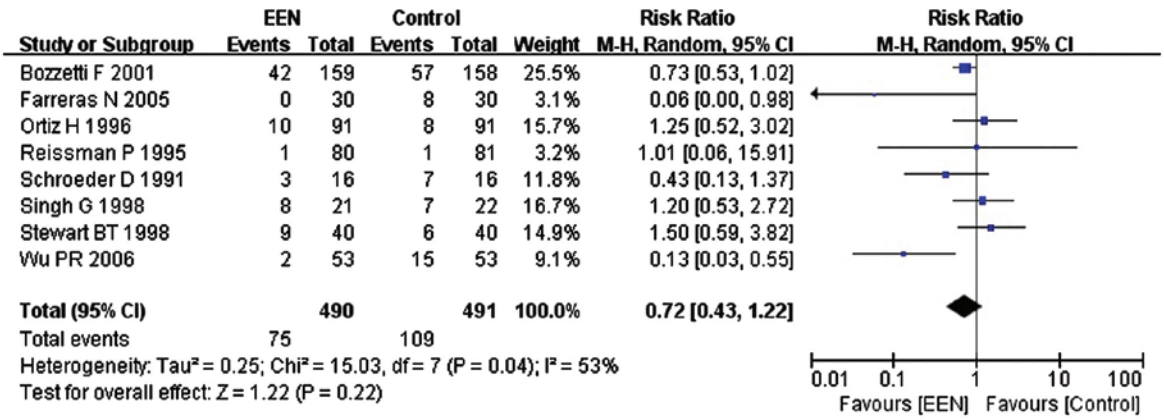

Figure 9. Forest plot of the non-infectious complications between the treatment [early enteral nutrition (EEN)] and control groups using the fixed-effects model. M-H: Mantel-Haenszel test; SD, standard deviation; CI, confidence interval.

Infectious complications. Our analysis using the fixed-effect model for infectious complications (I^2=35%; P>0.05; χ^2=10.75) suggested that, EEN was more effective in decreasing the incidence of infectious complications in comparison with control (RR=0.50, 95% CI: 0.38, 0.67; P<0.01) (Fig. 8).

Non-infectious complications. Our analysis revealed that the heterogeneity of non-infectious complications between the studies was significant (I^2=53%; P<0.05; χ^2=15.03). Thus, we performed a subgroup analysis and the subgroups were divided dependent on whether the EN or PN were added to the control group. I^2 between the subgroups was 0% (P=0.60; Chi^2=0.28). Consequently, the fixed-effects model was used. The results suggested that patients in the EEN group had a lower incidence of non-infectious complication (RR=0.72, 95% CI: 0.43, 1.22; P<0.05) than the control (Fig. 9).

Length of hospital stay. Five studies (20,23,24,26,27) comprising 587 subjects mentioned the length of hospital stay (day). I^2 between the studies was 76% (P<0.05; χ^2=16.67) and thus a random-effects model was used. Our analysis revealed no significant difference with respect to shortening the length of hospital stay between the EEN and control groupa (MD=-0.50, 95% CI: -1.56, 0.56; P>0.05) (Fig. 10). Furthermore, the asymmetry funnel plot suggested a possible publication bias existed between the studies in which patients mentioned the change of length of hospital stay (Fig. 11).

Discussion

Nutritional support is a vital part of the therapy of most surgical patients. Early initiation, particularly via the enteral route has a significant effect on postoperative recovery in a wide variety of patients (30). However, the physiological mechanisms underlying the beneficial effect of EEN have yet to be fully elucidated. Factors that may play a role include preservation of gut mass, prevention of increased gut permeability to bacteria and other toxins, and maintenance of the gut-associated lymphoid tissue (31). Classically, the term 'early' was defined as EN administration within postoperative day 3 (32); however, 'early' has been more recently redefined as EN administration within 24-48 h after admission or surgery (33). It appears that administration of nutrition within 24 h of major surgery, injury, or burn is ideal, but within 48 h is acceptable. However, hemodynamic stability is a prerequisite to the initiation of enteral feeding (34). RCTs included in the present meta-analysis administered EN support to patients within 12 or 24 h after digestive tract surgery.

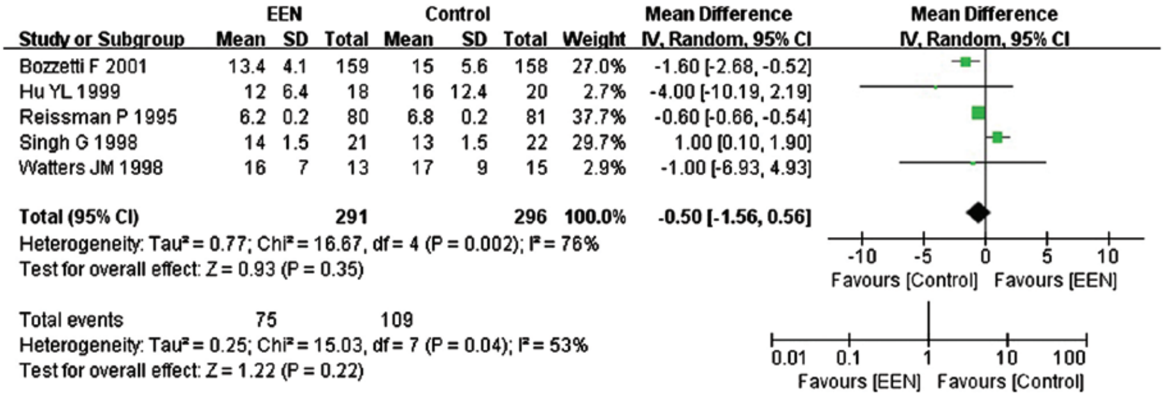

Figure 10. Forest plot of the length of hospital stay between treatment [early enteral nutrition (EEN)] group and control group: random-effects model. SD, standard deviation; CI, confidence interval.

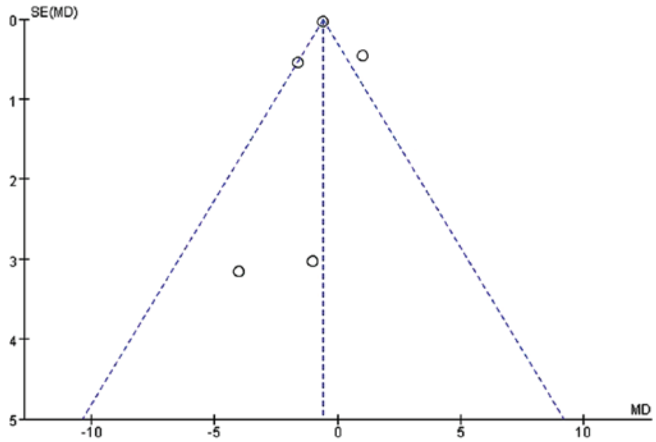

Figure 11. Funnel plot of studies mentioning the length of hospital stay between treatment (early enteral nutrition) group and control group. Dotted lines are pseudo 95% confidence intervals. SE, standard error; MD, mean difference.

Surgical patients usually present an intense metabolic state due to neuroendocrine stress, which may exacerbate protein catabolism developing negative nitrogen balance (35). Serum protein is an important indicator of the body's nutritional status. Serum albumin is the most abundant protein in blood plasma with a serum half-life of approximately 20 days, serving as a potential marker for nutritional status (36). The serum half-life of prealbumin is approximately 1.9 days, constituting it a sensitive marker of nutritional evaluation for a short period of time (37). In the present meta-analysis, although the administration of EEN had no significant effect on serum total protein, it significantly increased the levels of serum albumin and prealbumin, suggesting use of EEN benefited protein synthesis and wound healing, thereby improving the nutritional status of patients.

Previous findings have shown that PN induced an atrophy of the small intestinal mucosa due to a strong reduction in villi height and the crypt length, resulting in intestinal barrier dysfunction (38,39). Therefore, PN often induced enterogenic infection in patients with digestive tract surgery. EN support had fewer infectious complications than others by comparison. The rationale of nil by mouth and gastric decompression aims to prevent postoperative nausea and vomiting and protect anastomosis, thus allowing wound healing to occur prior to the body experiencing stress from food (40). Our meta-analysis revealed that EEN for patients with digestive tract surgery decreased the incidence of postoperative infectious and non-infectious complications effectively, suggesting EEN is important in protecting the intestinal barrier, improving immune function and reducing the incidence of postoperative infections. In addition, EEN administration for patients with digestive tract surgery resulted in shorter length of first bowel action after surgery. Thus, EEN may stimulate the growth of intestinal epithelial cells, regulate the neuroendocrine system and induce gut hormone secretion, and subsequently increased blood flow to vital organs of the digestive system for functional recovery (41-43). Furthermore, fiber in the EN may have also contributed to the gastrointestinal recovery after surgery (44). As for the length of hospital stay, the analysis showed no significant difference between the EEN and control groups.

The present meta-analysis has some limitations. First, the 11 included trials mentioned randomization and parallel control, but did not mention whether the studies were blinded, which affects the quality scores of the included trials. Second, the quality score of Bozzetti *et al* (27) was 3, but the number of enrolled subjects was large, which leads to uncertainty in biases to the final result of the present meta-analysis. Third, the variety of intervention in the control group and duration of nutrition support between the included trials may also affect the final results.

In conclusion, the results show that EEN for patients with digestive tract surgery improves the nutritional status, promotes the functional recovery of digestive system and reduces the risk of postoperative complications.

Acknowledgements

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