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Review Article

Perioperative pro-/synbiotic for colorectal surgery: a systematic review and updated meta-analysis of randomized controlled trials

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Abstract: Aim Perioperative pro-/synbiotic therapy is widely used in surgical patients to reduce infections and enhance recovery. However, it remains controversial when used in colorectal surgery. We performed this meta-analysis to assess the efficacy of perioperative pro-/synbiotic in colorectal surgery. Methods After the literature search of PubMed, Embase, Cochrane Library and Web of Science, a systematic review and meta-analysis were performed on randomized controlled trials. Quality assessment and data extraction were performed. The main outcomes included total postoperative infectious complications, pneumonia, wound infection, intra-abdominal abscess, urinary infection and length of hospital stay. Results: Thirteen trials (total, 1301 patients) were included based on the criteria. Perioperative pro-/synbiotic administration was associated with a significant reduction in total postoperative infectious complications (RR 0.58, 95% CI, 0.46 to 0.73, $P < 0.00001$), pneumonia (RR 0.31, 95% CI, 0.14 to 0.66, $P = 0.003$), wound infection (RR 0.66, 95% CI, 0.49 to 0.88 $P = 0.005$) and length of hospital stay (WMD -1.97, 95% CI, -3.44 to -0.50, $P = 0.009$) in patients undergoing elective colorectal surgery. No significant differences were found in the incidence of intra-abdominal abscess or urinary infection. Conclusion: Perioperative pro-/synbiotic administration in patients undergoing elective colorectal surgery appeared to improve clinical outcomes. Use of multiple trains should be recommended in future clinical practices.

Keywords: Probiotics, synbiotics, colorectal surgery, meta-analysis, randomized controlled trial

Introduction

Colorectal resection is the best treatment for a wide range of colorectal disease, especially for colorectal cancer (CRC) [1]. It is well known that with traditional perioperative care, patients undergoing elective colorectal resection can have a complication rate of 20% to 30% [2]. Many studies reported that preoperative preparation strategies and surgical trauma would break the intestinal microbial balance, restrain the gut barrier function and local immune function, aggravate systemic inflammation, and thus result in postoperative infectious complications [3, 4]. Postoperative infectious complication remains a major cause of prolonged length of hospital stay, an increase in medical costs, a poor postoperative life quality and various other problems in patients undergoing surgical procedures [5].

Probiotic is defined as live microorganisms in sufficient numbers that beneficially affect the host by implantation or colonization. Prebiotic is a non-digestible food supplement that selectively stimulates the growth and/or activity of bacteria in the colon. Synbiotic is a product which contains both pro- and prebiotics [6]. Many of the published researches have intensively investigated the effects of probiotics in vitro and animal models [7-9]. In recent years, several randomized trials have evaluated the effect of administration of pro-/synbiotic in some human gastrointestinal diseases [10-12]. So would pro-/synbiotic also have an effect on surgical patients? Probiotic therapy was first introduced that would improve clinical and laboratory outcomes of patients undergoing gastrointestinal surgery in 1965 [13]. Some studies reported that preoperative and postoperative probiotic therapy can improve the intestinal

Table 1. Full Search Strategy for PubMed

1. Probiotic* [Title/Abstract] OR synbiotic* [Title/Abstract] OR prebiotic* [Title/Abstract]
2. Laparoscopy [MeSH Terms] OR laparotomy [MeSH Terms]
3. Colorectal surgery [MeSH Terms] OR colectomy [MeSH Terms]
4. "Colon/surgery "[MeSH Terms]" OR "colonic diseases/surgery" "[MeSH Terms]" OR "rectal diseases/surgery" "[MeSH Terms]" OR "rectum/surgery" [MeSH Terms]
5. Resection OR surgery OR surgical OR laparoscop*
6. #2 OR #3 OR #4 OR #5
7. Colorect* OR colo* OR rect* OR sigmoid OR bowel OR intestin*
8. Colorectal neoplasms [MeSH Terms] OR cecal neoplasms [MeSH Terms]
9. #7 OR #8
10. #1 AND #6 AND #9
11. Randomized controlled trial [Publication Type]
12. Randomized [Title/Abstract]
13. Placebo [Title/Abstract]
14. Clinical trials as topic [MeSH Terms: noexp]
15. Randomly [Title/Abstract]
16. Trial [Title]
17. #11 OR #12 OR #13 OR #14 OR #15 OR #16
18. Animals [MeSH Terms] NOT humans [MeSH Terms]
19. #17 NOT #18
20. #10 AND #19

* means the omitted letters of the words.

microbial environment, enhance immune responses, attenuate systemic inflammatory responses and reduce postoperative complications in patients who undergoing liver transplant and upper gastrointestinal surgery [14-16]. A meta-analysis also showed that probiotic and synbiotic nutrition strategies reduce the incidence of postoperative sepsis in the elective general surgery [17].

For colorectal surgery, evidence from clinical studies about the effect of probiotics remains controversial. A previous meta-analysis has shown that perioperative pro-/synbiotic therapy is associated with a significant reduction of postoperative total infections, pneumonia, diarrhea and symptomatic intestinal obstructions [18]. However, as small numbers of included studies, evidence has not been strong enough. A recent clinical trial even indicated that probiotics did not reduce the rates of incisional surgical-site infection and even increased rates of leakage [19], while another clinical trial indicated that a probiotic formulation significantly decreased the risk of postoperative complications such as infections and anastomotic leakage [20]. With more and more recent randomized controlled trials (RCTs) comparing pro-/synbiotics with traditional care in patients undergoing colorectal surgery were published, we performed this meta-analysis to assess the efficacy of perioperative pro-/synbiotic administration in patients undergoing elective colorectal surgery, based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [21]. If any, this may justify the positive effect of perioperative pro-/synbiotic administration in the future.

Materials and methods

Literature search

Studies published up to October 2015 were searched in PubMed, Embase, Cochrane Library and Web of Science. No language restrictions were applied. Two reviewers (W.Z. Chen and J.X. Lu) generated the search strategy. We also searched unpublished trials and conference proceedings through the System for Information on Grey Literature in Europe, the National Research Register (UK) and International Clinical trials Registry Platform in case to prevent clinical trials which meet the criteria from being omitted. First, article titles and abstracts were screened, and then full texts were reviewed independently by two investigators (W.Z. Chen and J.X. Lu). Discrepancies were resolved by the reviewers. If a consensus could not be reached between the first two reviewers, a third reviewer (L.F. Ding) would take part in the discussion to resolve conflict. The literature search strategy for PubMed was showed in **Table 1**.

Inclusion and exclusion criteria

From the eligible studies, we selected RCTs with the use of a probiotic, prebiotic, or synbiotic agent in adult patients (aged > 18 years) undergoing elective colorectal surgery. Studies were required to report at least one of the outcome measures mentioned below. When more than one version of the same study was found, only the most recent version or the one with complete data was included. In case of disagreement, full texts were obtained for final judgment by two reviewers (W.Z. Chen and J.X. Lu); otherwise a third reviewer (L.F. Ding) would take part in the discussion as a referee.

Excluded studies 1) were classified as non-RCTs (such as nonrandomized, quasi-randomized, pseudo-randomized, clinical controlled trials or cohort or retrospective studies); 2) were with patients received chemotherapy or radiotherapy; 3) involved emergency surgery or pediatric surgery.

Data extraction and outcomes

Two reviewers (W.Z. Chen and J.X. Lu) extracted all relevant data from each eligible study using a standardized reporting form independently. Discrepancies were resolved by discussion between the reviewers and review of the original articles. Extracted information from each eligible study included 1) study information, including name of the first author, year of publication, country, number of patients in each group, length of treatment, type of intervention and control; 2) patient information including age, sex and type of surgery; 3) outcome measures.

Primary outcome measures included 1) incidence of total postoperative infectious complications (defined as any infectious complication reported within the postoperative period), pneumonia, wound infection, intra-abdominal abscess and urinary infection; 2) the numbers of bacteria (including Enterobacteriaceae, Bifidobacterium, Lactobacillus, and Enterococcus) in the postoperative fecal bacterial colonies; 3) the culture of mesenteric lymph nodes (MLN) for bacterial translocation (BT) (defined as the percentage of positive culture in MLN).

Secondary outcome measures included 1) time to first passage of flatus and stool and 2) length of hospital stay (LOS, defined as the number of days in hospital after surgery until discharge).

Assessing quality of trials

The quality of methodology of the included studies was assessed independently by two reviewers (W.Z. Chen and J.X. Lu) with the use of the Cochrane Collaboration's risk of bias tool [22]. In addition, a previously validated score called Jadad Scale was used to evaluate the quality of RCTs [23]. The total score ranges from 0 to 5, with 5 being optimal. Studies scoring 3 to 5 are considered to be of higher quality.

Statistical analysis

For continuous outcome data, means and standard deviations (SD) were used to calculate a weighted mean difference (WMD) in the meta-analysis. Data reported as medians and ranges or medians and interquartile ranges were converted to means and SD by some formulas [24]. For dichotomous outcomes, the relative risk (RR) was calculated. Data were analyzed using Review Manager software version 5.0 from the Cochrane Collaboration. Effect estimates were presented with 95% confidence intervals (CIs). The presence and amount of heterogeneity was tested using Q test and I^2 index [25], $P < 0.1$ denoted the presence of significant heterogeneity. Subgroup analyses were performed based on type of strain (multiple or single) and time of pro-/synbiotic administration (perioperative or pre-/postoperative). The fixed-effects model was used when there was little evidence of heterogeneity; otherwise, a random-effects model was used. Funnel plots were used to assess the potential publication bias. For all comparisons, statistical significance was defined as $P < 0.05$ and all tests were two-sided.

Results

Included studies

The initial literature search identified 1400 potentially relevant studies, of which 1387 were excluded owing to the exclusion criteria or other insufficient details. Thirteen RCTs were included in the meta-analysis (**Figure 1**) [4, 19, 20, 26-35]. These studies were published between 2007 and 2015, with a total of 1301 patients, ranging from 18 to 362 patients. Only two of the included studies were multiple-center studies, others were studied in single center. The RCTs scored a mean of 4.0 (range 3-5)

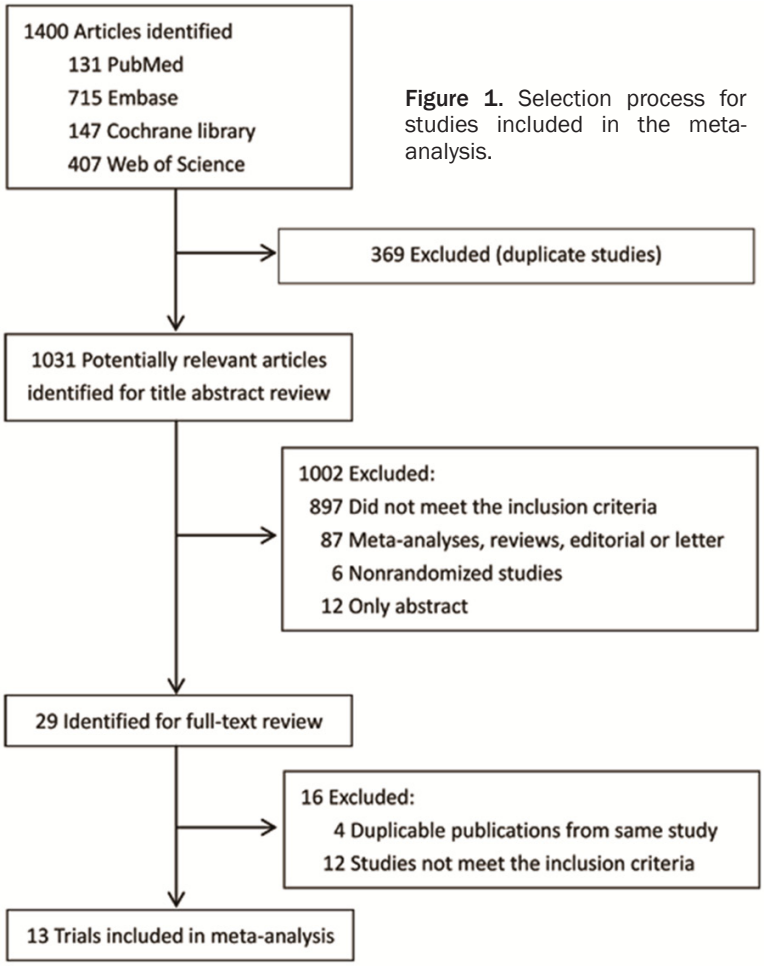

Figure 1. Selection process for studies included in the meta-analysis.

on the Jadad Scale. The characteristics of the included studies are showed in **Table 2**.

Figure 2 shows evaluation of risk of bias for the included studies. Six studies were adequate in random sequence generation, five studies were unclear; allocation concealment was adequate in five studies and unclear in six studies; four studies were double blind and adequate in blinding of outcome assessment; seven of included studies were at low risk of bias for incomplete outcome data and ten were at low risk of bias for selective reporting. All of the included trials were completely free from other bias.

Primary outcome measures

The results from meta-analysis of primary outcome measures were showed in **Table 3**. The incidence of total postoperative infectious complications was reported in nine studies [4, 19, 20, 27-29, 33-35]. Patients in the pro-/synbiotic group had a significantly fewer total postoperative infectious complications (nine RCTs, 1138 patients, RR 0.58, 95% CI, 0.46 to 0.73, $P < 0.00001$), with little evidence of heterogeneity between trials ($\chi^2 = 12.76$, $P = 0.12$, $I^2 = 37\%$) (**Figure 3**). There were lower incidence of pneumonia in the pro-/synbiotic group (five RCTs, 480 patients, RR 0.31, 95% CI, 0.14 to 0.66, $P = 0.003$), with little evidence of heterogeneity between trials ($\chi^2 = 1.24$, $P = 0.87$, $I^2 = 0\%$) [4, 20, 28, 29, 33] (**Figure 4**). There were lower incidence of wound infection in the pro-/synbiotic group (eight RCTs, 1105 patients, RR 0.66, 95% CI, 0.49 to 0.88 $P = 0.005$), with little evidence of heterogeneity between trials ($\chi^2 = 6.71$, $P = 0.46$, $I^2 = 0\%$) [4, 19, 20, 27-29, 33, 34] (**Figure 5**). However, there were no statistically significant differences in intra-abdominal abscess [4, 19, 20, 28, 29, 35] or urinary infection [20, 28, 33, 35] (six RCTs, 558 patients, RR 0.58, 95% CI, 0.26 to 1.28, $P = 0.18$, $I^2 = 0\%$; four RCTs, 411 patients, RR 0.55, 95% CI, 0.26 to 1.17, $P = 0.12$, $I^2 = 32\%$; respectively).

Four studies involved the applicable data on postoperative fecal bacterial colonies (**Figure 6**). Overall, the numbers of Enterobacteriaceae were significantly lower in the pro-/synbiotic group (four RCTs, 215 patients, WMD -0.79, 95% CI, -1.39 to -0.20, $P = 0.009$), with some evidence of heterogeneity between trials ($\chi^2 = 36.40$, $P < 0.00001$, $I^2 = 92\%$) [26, 28-30]. However, there were no apparently differences in the numbers of Bifidobacterium [29, 30], Lactobacillus [26, 28, 30] or Enterococcus [26, 30] (two RCTs, 120 patients, WMD 2.69, 95% CI, -1.64 to 7.02, $P = 0.22$, $I^2 = 100\%$; three RCTs, 155 patients, WMD 1.93, 95% CI, -1.43 to 5.29, $P = 0.26$, $I^2 = 99\%$; two RCTs, 91 patients, WMD 1.42, 95% CI, -2.35 to 5.18, $P = 0.46$, $I^2 = 99\%$; respectively).

Table 2. Characteristics of the included studies

Reference	No. of patients		Age (years)		Sex (M/F)		Intervention group	Length of treatment (days)	Control group	Type of surgery	Jadad score
	IG	CG	IG	CG	IG	CG					
Reddy 2007 (United Kindom)	20	22	68.5 (62.5-74)	72.5 (53-81)	9/11	13/9	La5, L. bulgaricus, BB-12 and S. thermophilus	NR	Neomycin + MBP	RHC, LHC, AR, APR, HP, SC, PPC	4
Gianotti 2010 (Italy)	21	10	63.7 (6.3)	63.3 (10.2)	15/6	7/3	La1 and BB536	6	placebo	LHC, RHC, AR	5
Horvat 2010 (Slovenia)	48	20	62 (29-86)	65 (52-78)	19/29	11/9	multi-strain/-fiber Synbiotic 2000™	3	oral solution	LHC, RHC, RTC, RSR, LAR	4
Mangell 2012 (Sweden)	32	32	74 (70-80)	70 (64-79)	16/16	20/12	Lp 299v	13	placebo	LHC, RHC, IR, RTC, RSR, PPC	4
Zhang 2012 (China)	30	30	67.5 (45-87)	61.5 (46-82)	10/20	14/16	BB536, La 5 and E. faecalis	3	placebo	LHC, RHC, RSR, AR, APR	4
Zhu 2012 (China)	30	30	61.2 (10.5)		36/24		BB536, La 5 and E. faecalis	12	MBP	LCRS	3
Krebs 2013 (Slovenia)	38	16	65 (43-87)		21/33		lactobacilli and prebiotics	3	MBP	SR, LHC, RHC, AR, RTC	3
Pellino 2013 (Italy)	10	8	71.5 (2.1)	72.9 (1.6)	5/5	4/4	S. thermophiles, B., Lattobacilli	28	placebo	LCRS	3
Liu 2013 (China)	75	75	66.06 (11.02)	62.28 (12.41)	38/37	40/35	L. plantarum, L. acidophilus-11 and B. longum-88	16	placebo	RTC, RHC, SR, AR	5
Sadahiro 2014 (Japan)	100	95	67 (9)	66 (12)	49/51	51/44	Bifidobacteria	17	NR	LHC, RHC, RTC, LCRS	4
Kotzampassi 2015 (Greece)	84	80	65.9 (11.5)	66.4 (11.9)	57/27	58/22	La 5, Lp, BB-12 and Sb	16	placebo	LAR, RSR, RHC, TC	5
Komatsu 2015 (Japan)	168	194	66.7 (11.6)	67.7 (10.7)	92/76	118/76	L. casei and B. breve	13-17	NP	RHC, LHC, LAR, APR	4
Consoli 2015 (Brazil)	15	18	51 (28-76)	59 (17-83)	5/10	10/8	S boulardii	7	NP	RHC, LHC, TC	4

Values in brackets are either SD or a range. IG = Intervention group; CG = Control group; NR = Not report; NP = No placebo; L. = Lactobacillus; B. = Bifidobacterium; E. = Enterococcus; S. = Streptococcus; La1 = L. johnsonii; La5 = L. acidophilus; BB-12 = B. lactis; BB536 = B. longum; Lp 299v = Lactobacillus plantarum 299v; Sb = Saccharomyces boulardii; RHC = Right hemicolectomy; LHC = Left hemicolectomy; AR = Anterior resection; APR = Abdominoperineal resection; HP = Hartmann's procedure; SC = Subtotal colectomy; PPC = Panproctocolectomy; RTC = Resection of transverse colon; RSR = Rectosigmoid resection; LAR = Low anterior resection; IR = Ileocecal resection; LCRS = Laparoscopic colorectal surgery; SR = Sigmoid resections; TC = Total colectomy.

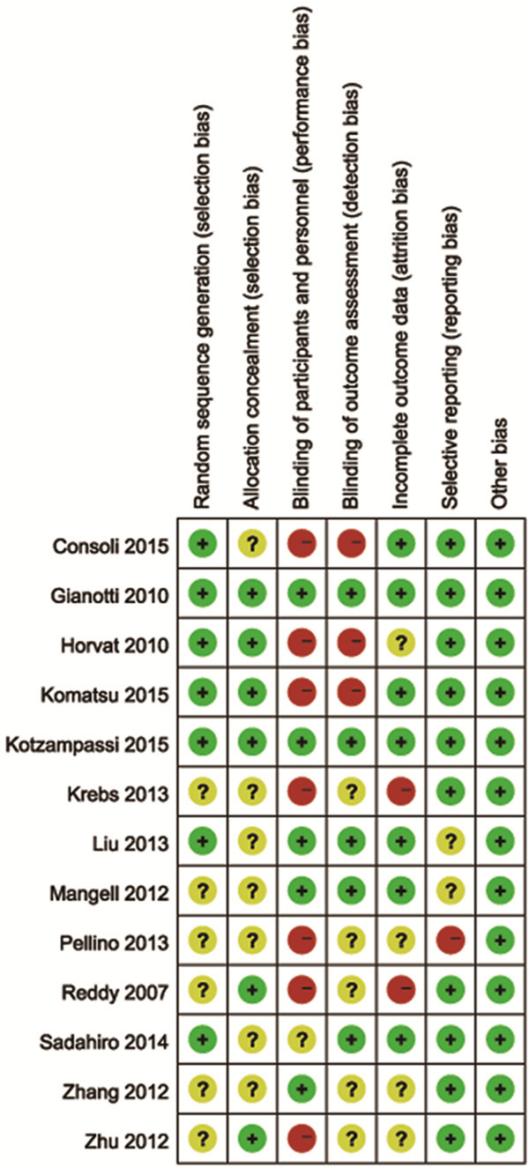

Figure 2. Assessment of risk of bias in included studies.

There was no significant difference in the culture of MLN for BT compared with the control group (three RCTs, 238 patients, RR 0.52, 95% CI, 0.13 to 1.98, $P = 0.34$, $I^2 = 79\%$) [4, 28, 33].

Secondary outcome measures

Table 4 showed the results from meta-analysis of secondary outcome measures. The time to first passage of flatus and stool was reported in two studies [28, 31]. LOS was reported in another two studies [29, 32]. There was a significantly shorter time to first passage of flatus and LOS in the pro-/synbiotic group (two RCTs, 118 patients, WMD -0.67, 95% CI, -1.05 to -0.29, $P = 0.0006$, $I^2 = 0\%$; two RCTs, 78 patients, WMD -1.97, 95% CI, -3.44 to -0.50, $P = 0.009$, $I^2 = 0\%$; respectively). However, there was no significant difference in the time to first passage of stool (two RCTs, 118 patients, WMD 0.17, 95% CI, -0.31 to 0.65, $P = 0.49$, $I^2 = 0\%$).

Subgroup analysis

For subgroup analysis based on multiple or single strain(s), only in the multiple strains subgroup, there was a significant reduction in total postoperative infectious complications ($P < 0.00001$, $I^2 = 36\%$ vs. $P = 0.30$, $I^2 = 0\%$), pneumonia ($P = 0.002$, $I^2 = 0\%$ vs. $P = 1$), wound infection ($P = 0.001$, $I^2 = 0\%$ vs. $P = 0.99$, $I^2 = 0\%$), urinary infection ($P = 0.03$, $I^2 = 29\%$ vs. $P = 0.33$, $I^2 = 0\%$) and the numbers of Enterobacteriaceae in the postoperative fecal bacterial colonies ($P < 0.00001$, $I^2 = 80\%$ vs. $P = 0.71$), and a significant increase in the numbers of Lactobacillus in the postoperative fecal bacterial colonies ($P = 0.04$, $I^2 = 98\%$ vs. $P = 0.10$). Due to the limited data, the subgroup analyses were not performed in other outcomes (**Figures 3**-**6**).

Publication bias

The funnel plot was not synthesized to determine the presence of publication bias due to the limited number of trails included in this meta-analysis.

Discussion

The results of this meta-analysis suggested that perioperative pro-/synbiotic administration is associated with a significant reduction in total postoperative infectious complications, pneumonia, wound infection, the numbers of Enterobacteriaceae in the postoperative fecal bacterial colonies, the time to first passage of flatus and length of hospital stay in patients undergoing elective colorectal surgery.

The present study was based on 13 RCTs, 1301 patients in total. There has been one previously published meta-analysis about the effect of probiotics on colorectal resection [18]. As the increased number of included studies could enhance the quality of evidence [36], the updated meta-analysis included 13 studies, and 9 of these studies (1102 patients) were published after the previous published meta-

Table 3. The results from meta-analysis of primary outcome measures

Groups	No. of studies	95% CIs	Statistical method	*P*-value	HG *P*-value
Infectious complications					
Total infectious complications	9	0.58 [0.46, 0.73]	RR (Fixed)	< 0.00001	0.12
Pneumonia	5	0.31 [0.14, 0.66]	RR (Fixed)	0.003	0.87
Wound infection	8	0.66 [0.49, 0.88]	RR (Fixed)	0.005	0.46
Intra-abdominal abscess	6	0.58 [0.26, 1.28]	RR (Fixed)	0.18	0.52
Urinary infection	4	0.55 [0.26, 1.17]	RR (Fixed)	0.12	0.22
Fecal bacterial colonies					
Enterobacteriaceae	4	-0.79 [-1.39, -0.20]	WMD (Random)	0.009	< 0.00001
Bifidobacterium	2	2.69 [-1.64, 7.02]	WMD (Random)	0.22	< 0.00001
Lactobacillus	3	1.93 [-1.43, 5.29]	WMD (Random)	0.26	< 0.00001
Enterococcus	2	1.42 [-2.35, 5.18]	WMD (Random)	0.46	< 0.00001
Culture of MLN for BT	3	0.52 [0.13, 1.98]	RR (Random)	0.34	0.009

RR = Relative risk; WMD = Weighted mean difference; HG = Heterogeneity; POD = Postoperative day; MLN = Mesenteric lymph nodes; BT = Bacterial translocation.

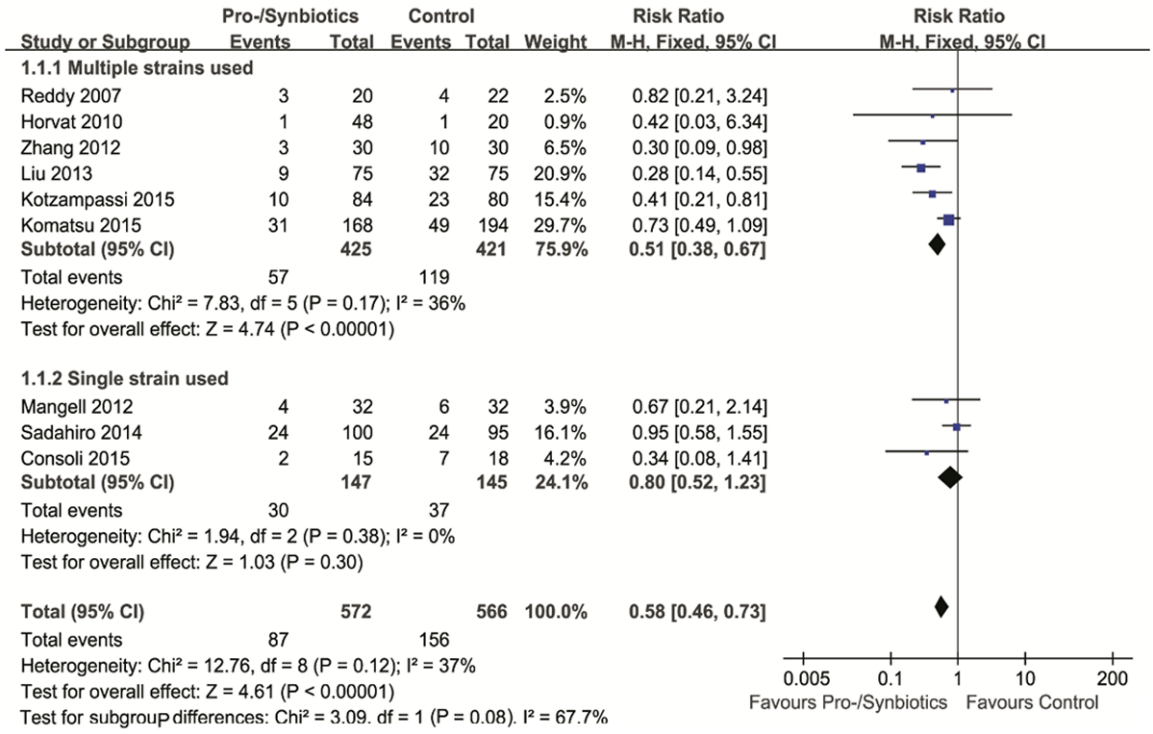

Figure 3. Forest plot for effect of pro-/synbiotics on the total postoperative infectious complications (subgroup analysis based on multiple or single strain(s)) M-H = Mantel-Haenszel test.

analysis. The present study is the first meta-analysis to demonstrate that perioperative pro-/synbiotic administration is associated with a significant reduction in the wound infection and a significantly shorter time to first passage of flatus and length of hospital stay in patients undergoing elective colorectal surgery.

Perioperative pro-/synbiotic administration was reported to have positive effect on different surgical patients. When it was used in patients undergoing surgery in the upper gastrointestinal tract or liver transplantation, the results showed a reduction in rate of postoperative infections [37, 38]. In this meta-analysis, we

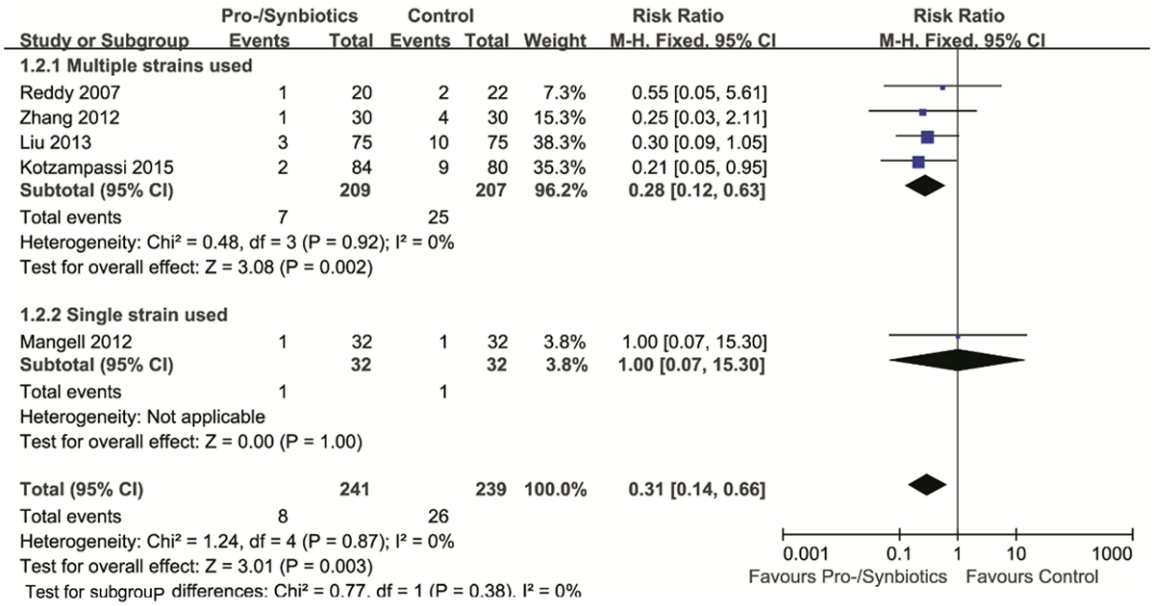

Figure 4. Forest plot for effect of pro-/synbiotics on the pneumonia (subgroup analysis based on multiple or single strain(s)). M-H = Mantel-Haenszel test.

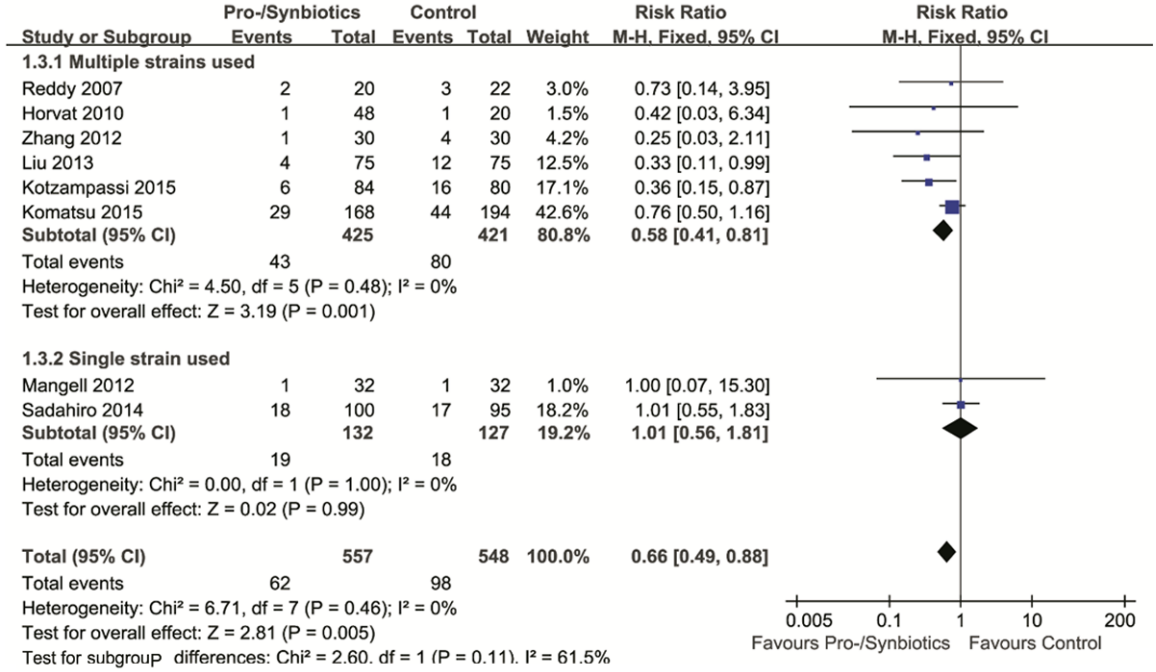

Figure 5. Forest plot for effect of pro-/synbiotics on the wound infection (subgroup analysis based on multiple or single strain(s)). M-H = Mantel-Haenszel test.

found that the perioperative use of pro-/synbiotics was beneficial in reducing the incidence of total postoperative infectious complications, pneumonia and wound infection. In addition, results from subgroup analysis showed that the use of multiple strains seemed to have beneficial effects on total postoperative infectious complications, pneumonia, wound infection and urinary infection. However, some latest clinical trials included in the present meta-anal-

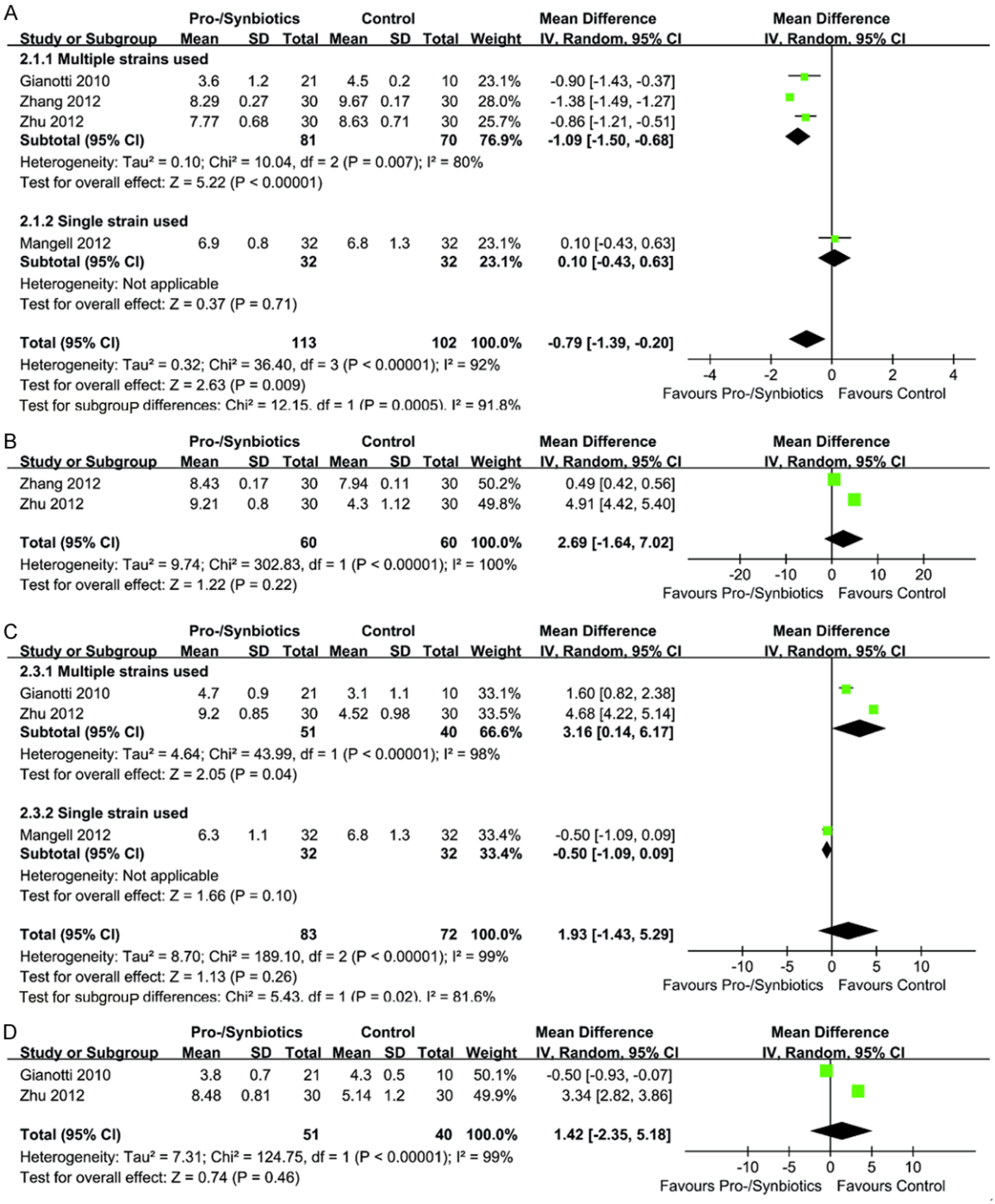

Figure 6. Forest plot for effect of pro-/synbiotics on postoperative fecal bacterial colonies (subgroup analysis based on multiple or single strain(s)). A. Enterobacteriaceae, B. Bifidobacterium, C. Lactobacillus, D. Enterococcus. M-H = Mantel-Haenszel test.

ysis had a contrary conclusion, indicating that probiotics did not significantly prevent infection after elective colon cancer surgery [19, 34, 35]. The inconsistent effects of pro-/synbiotics on the reduction of postoperative infection rate in different surgeries could be explained in two aspects. First, the conditions for use of probiotics or synbiotics in colon or rectum might be different from other digestive organs such as the upper gastrointestinal tract, pancreas, and liver, because the number of mucosa-associated bacteria in colon and rectum plays an impor-

Table 4. The results from meta-analysis of secondary outcome measures

Groups	No. of studies	95% CIs	Statistical method	*P*-value	HG *P*-value
Time to first passage of flatus	2	-0.67 [-1.05, -0.29]	WMD (Fixed)	0.0006	0.44
Time to first passage of stool	2	0.17 [-0.31, 0.65]	WMD (Fixed)	0.49	0.55
Length of hospital stay	2	-1.97 [-3.44, -0.50]	WMD (Fixed)	0.009	0.88

WMD = Weighted mean difference; HG = Heterogeneity.

tant role in bacterial translocation and infections. Second, it has been reported that *Lactobacillus plantarum 299v* did not have any protective effects against wound infection in surgical patients [39]. However, a latest clinical trial had provided a probiotic formulation which could significantly decrease the risk of postoperative complications [20]. It is well accepted that different species and strains probiotics could be activated through various mechanisms, which means their gastrointestinal survivability, modulation of intestinal flora or immune activities may vary depend on their composition [40]. To date, the exact pathophysiological mechanism for reduced pneumonia and wound infection due to perioperative pro/synbiotic administration is yet to be identified [41]. As probiotics have been showed to attenuate BT [15], we deduced that perioperative pro/synbiotic administration appears to reduce the incident of postoperative pneumonia and wound infection by preventing bacterial translocation in the patients undergoing colorectal surgery.

Substantial statistical heterogeneity was detected in the analysis of postoperative fecal bacterial colonies and the culture of MLN for BT. In order to explore the sources of heterogeneity, subgroup analysis based on multiple or single strain(s) and perioperative or pre-/postoperative pro-/synbiotic administration were performed. However, subgroup analysis could not explore the sources of heterogeneity in the analyses of the postoperative fecal bacterial colonies and the culture of MLN for BT. As these two outcomes were measured in the laboratory, so the differences in testing methods may contribute to the heterogeneity of these two outcomes. In addition, apart from type of strain and time of pro-/synbiotic administration, some other clinical heterogeneity still existed between the included studies, such as different dose of pro-/synbiotic and use of MBP before surgery. There was no reporting of a guideline of perioperative pro-/synbiotic administration in patients undergoing elective colorectal surgery in these studies. We wish the present meta-analysis could give a strong evidence for the guideline of perioperative pro-/synbiotic administration in the future. MBP has been one of the routine preoperative preparation strategies for colorectal cancer surgery for many years and medical care guidelines consent to this regimen, even though controversy surrounds it [42]. However, many previous meta-analyses showed that MBP had the futility in reducing postoperative complications and motility [43, 44]. So MBP had less influence on our meta-analysis.

There were several limitations to the present meta-analysis. First, the evidence of some outcome measures seemed not to be at high level because of the limited data in the included studies. However, we had made a comprehensive literature search to extract all useful data and the sample size was large in the analyses of most primary outcomes. Second, the included studies were unable to determine which specific strain is the most effective. Third, some studies included in this meta-analysis had small sample size, indicating that the reliability and validity of the conclusions might be influenced to a certain extent. Fourth, the publication bias probably exists owing to the limited number of trails, so we enhanced our literature search to minimize publication bias. Finally, across the included studies, there was not a standardized reporting of surgical methodology. The variability in surgical technique may influence the gut flora unintentionally. Due to these limitations, our conclusions were made prudently.

Conclusions

In summary, despite the limitations in the included studies, the evidence from the present meta-analysis showed perioperative pro-/synbiotic administration may prevent total postoperative infectious complications, pneumonia

and wound infection, reduce the time to first passage of flatus and length of hospital stay in patients undergoing colorectal surgery. Use of multiple trains should be recommended in future clinical practices. Further clinical trials should be well-designed to make a precise therapeutic schedule about optimal type dosage and administration time to assess the efficacy and safety of pro-/synbiotics.

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Disclosure of conflict of interest

None.

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