Journal of Gastroenterology and Hepatology JGHF

doi:10.1111/jgh.12206

META-ANALYSIS AND SYSTEMATIC REVIEW

Chewing gum reduces postoperative ileus following abdominal surgery: A meta-analysis of 17 randomized controlled trials

Shan Li, Yanqiong Liu, Qiliu Peng, Li Xie, Jian Wang and Xue Qin

Department of Clinical Laboratory, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, China

Key words
abdominal surgery, chewing gum, postoperative ileus.

Accepted for publication 16 March 2013.

Correspondence
Professor Xue Qin, Department of Clinical Laboratory, First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China. Email: qinxue919@yahoo.cn; Professor Shan Li, Department of Clinical Laboratory, First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China. Email: lishan8858@163.com

Shan Li, Yanqiong Liu contributed equally to this study and should be considered as co-first authors.

Competing interest: The authors declared that they have no conflict of interest in relation to this study.

Abstract

Background and Aim: Chewing gum proposal has been used in surgery to reduce postoperative ileus for more than 10 years; however, the efficacy remains imprecise. The aim of this study was to accurately assess whether the use of the chewing gum could reduce duration of postoperative ileus following the abdominal surgery.
Methods: A systematic review was conducted in Medline, EMBASE, and the Cochrane Library through December 2012 to identify randomized controlled trials comparing with and without the use of chewing gum in patients undergoing abdominal surgery. The outcome of interest was time to flatus, time to bowel movement, and length of stay. Subgroup analyses were performed to examine the impact of different studies structural design. Cumulative meta-analyses were used to examine how the evidence has changed over time.
Results: Seventeen randomized controlled trials involving 1374 participants were included. Overall time (in days) for the patients to pass flatus (weighted mean difference [WMD], −0.31; 95% confidence interval [CI], −0.43 to −0.19; $P = 0.000$); time to bowel movement (WMD, −0.51; 95% CI, −0.73 to −0.29; $P = 0.000$); and length of stay (WMD, −0.72; 95% CI, −1.02 to −0.43; $P = 0.000$) were significantly reduced in the treatment group. However, both of these results demonstrated significant heterogeneity. No evidence of publication bias was observed. Cumulative meta-analysis showed that chewing gum reduces duration of postoperative ileus that has been available for over 6 years.
Conclusions: Results of the meta-analysis suggest that chewing gum following abdominal surgery offers benefits in reducing the time of postoperative ileus.

Introduction

Postoperative ileus (POI) has been considered a temporary disturbance in gastric and bowel motility following abdominal surgery.[1,2] Almost all patients develop POI after abdominal surgery.[3,4] It is characterized by a transient cessation of bowel function, lack of bowel sounds, accumulation of gastrointestinal gas and fluid, pain and abdominal distention, nausea, vomiting, and delayed passage of flatus and stool.[1,2,5] The traditional end point of POI is the passage of flatus or a bowel movement. In general, operations that involve large incisions, extensive manipulation of the intestines, or exposure of the peritoneum to irritants such as blood or pus are more likely to result in POI.[1] The contributing factors of POI are varied, including pharmacologic, inflammatory, hormones, metabolic, gastrointestinal physiology, neurologic, psychological, and miscellaneous.[1] POI may extend length of hospital stay (LOS) 5 days longer than those without POI[6] and increase the expenditure of care by as much as between $750 million and $1 billion in the United States.[4,6,7] Safely shortening LOS and reducing the duration of POI are associated with improvement in the level of care provided as well as a significantly economic saving.

In order to reduce the duration of POI, various tactics such as a less invasive surgical procedure (e.g. laparoscopy), epidural anesthesia, early ambulation, nasogastric tube decompression, and early oral intake have been used in clinical setting.[8] But these methods should be have limited effect because the high incidences of POI have not been absolutely solved. Moreover, a meta-analysis by Vermeulen *et al.* [9]suggested that routine nasogastric tube placement serves no benefit on gastrointestinal functions and may even be harmful in patients after modern abdominal surgery.[9] Also, it is uncomfortable. A new approach that emphasizes patient comfort and based on available evidence should be considered. Sham feeding has been reported to stimulate bowel motility in humans.[10,11] Chewing gum is a type of sham feeding that simulates food ingestion. The reduction duration of POI afforded by chewing gum is supported by several studies.[12–25] However, other studies have obtained null results.[26–32] These discrepant evidences leave uncertainty in the surgical field about the efficacy of chewing gum in reducing the duration of POI. Several meta-analyses[33–37] showed a favorable effect of gum chewing on time to flatus and defecation, but all of these studies were small number size(less than 9 trials) and the results were not robust. Accordingly, we performed a systematic meta-analysis of randomized controlled trials (RCTs) to critically evaluate whether chewing gum reduces the duration of POI after abdominal surgery. If any, this may bring in providing an inexpensive, well-tolerated, and widely available solution to ameliorate an old problem.

Methods

We attempted to follow the proposals Quality of Reports of Meta-Analyses of Randomized Controlled Trials: the QUOROM statement to report our meta-analysis.[38]

Search strategy. Electronic databases MEDLINE, EMBASE, and Cochrane Library were used to search for RCTs up to December 2012. The final search strategy used for each database was based on key words both alone and combinations of the terms "chewing gum" and "surgery." A manual search of the reference lists of relevant articles was performed. A systematic search of Google Scholar was used to explore the gray literature. No language or time restrictions were made. Two reviewers (Yanqiong Liu and Li Shan) independently evaluated all retrieved articles using prespecified eligibility criteria. Disagreements were resolved by consensus. When a study reported the results on different indication of surgery, we treated it as separate studies in the meta-analysis.

Eligibility criteria. Studies were considered eligible if they met the following inclusion criteria: (i) Study design: randomized and controlled; (ii) Population: patients undergoing abdominal surgery; (iii) Intervention: use of chewing gum in the postoperative period; (iv) Comparator: standard postoperative care; (v) Outcome: report at least one of time to flatus, time to bowel movement, and hospital LOS. We did not use an age criterion and any minimum number of patients for inclusion in this meta-analysis.

Studies were excluded if any of the following existed: (i) nonrandomized study design; (ii) surgeries that did not involve abdominal surgery; (iii) primary outcome was not the interest of ours; (iv) interventions other than chewing gum; (vi) raw data could not be extracted in the appropriate format and failed to be obtained from the authors or other published results.

Data extraction. Information was carefully extracted from all eligible publications by two investigators (Li Shan and Yanqiong Liu) independently according to the inclusion criteria listed earlier. Any disagreements were resolved by discussion during a consensus meeting with a third reviewer (Qin Xue). The data extracted included first author's last name, year of publication, country, type and indication of surgery performed, total numbers of cases and controls, patient demographics for treatment and control groups (e.g. gender distribution, mean age), duration of operation time, time of gum chewing, rate of complications, quality indicators (e.g. details of randomization, blinding of patients), time to flatus, time to bowel movement, and LOS for treatment and control groups.

Risk of bias assessment. The risk of bias of each eligible study was assessed by two authors (Yanqiong Liu & Shan Li) using the Cochrane Risk of Bias tool[39] for RCTs. Disagreements were discussed with a third author (Xue Qin) and resolved by consensus. The instruments are described in detail elsewhere.[39]

Statistical analysis. Weighted mean differences (WMDs) together with their corresponding 95% confidence intervals (CIs) were estimated using a random-effects model.[40] Statistical heterogeneity was assessed by visual inspection of forest plots, by performing the χ^2 test (assessing the *P*-value) and by calculating the I^2 statistic.[41,42] If the *P*-value was less than 0.10 and I^2 exceeded 50%, indicating the presence of heterogeneity, a random-effects model (the DerSimonian and Laird method) was used;[43] otherwise, the fixed-effects model (the Mantel and Haenszel method) was used.[44] Publication bias was evaluated by constructing a funnel plot with visual assessment of asymmetry.[45,46] Subgroup analyses were carried out to examine whether the duration of POI varied by type of surgery, the indication of surgery, or Jadad quality. Sensitivity analysis was also performed to examine whether the effect estimate was robust to exclusion of different criterion. Cumulative meta-analysis was conducted to examine how the evidence has changed over time. A P-value < 0.05 was considered statistically significant. All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Literature search. A flow chart showing the study selection is presented in Figure 1. The study by Choi *et al.*[22] performed open and laparoscopic cystectomy, published its result in median and range rather than mean and SDs, and was subsequently excluded as we were unable to obtain these data from the authors. The study by Matros *et al.*[27] published median end points rather than the mean, but we can obtain appropriate data for time to first flatus and LOS from the published meta-analysis.[37] We could not get the full text or abstract of one citation[47] mentioned in the previous meta-analysis[36] to extracted original data, so it was excluded. Finally, 17 studies[12–14,16–21,23,24,26–31] were included in our meta-analysis.

Study characteristics. The characteristics of the included 17 RCTs are presented in Table 1. These studies were published between 2002 and 2012. Five studies were conducted in the United States, three in Europe, seven in Asia, and two in Africa. A total of 686 patients were in the treatment group and 688 in the control. Operations were performed via open surgery,[13,14,17–20,23,24,27,28,30] laparoscopic techniques,[12] or both,[26,31] not clearly stated.[16,29] Studies by McCormick *et al.*[26] and Crainic *et al.*[31] reported their open and laparoscopic surgery results separately, enabling

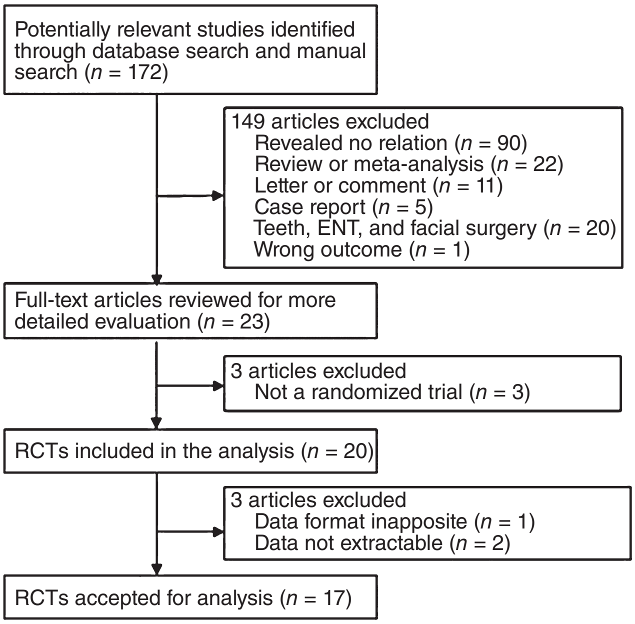

Figure 1 Quorum flow diagram depicting process of study selection. ENT, ear, nose, and throat; RCTs, randomized controlled trials.

calculation of their outcomes independently. All the included trials informed primary outcomes of time to first flatus; 14 trials documented time to first bowel movement and 13 trials documented LOS. The units of outcomes reported were variable and all were converted to days to allow uniform analysis. There was variation in the indications of surgery; seven studies were colectomy,[12–14,26–28,31] four studies were cesarean section,[17,18,20,23] and the remaining five studies (gastrectomy, gastrointestinal surgery, intestinal resection, appendectomy, ileostomy) were defined as others for small trial size. In two trials,[16,30] the gastrointestinal surgeries were done on children.

Risk of bias. The results of the risk of bias assessments are reported in Figure 2. Overall, all studies had low risk of bias. Only one trial was at high risk of bias for sequence generation (not truly random), which was randomized based on hospital record number.[19] But the method of randomization was unclear (not reported) in five trials.[12,13,16,26,30] Allocation concealment was stated clearly only in five trials.[17,20,23,27,28] Blinding of observers was part of the trial design in five studies,[20,23,27,28,30] but only one trial was double blinded with a placebo group.[27] Only one trial reported incomplete outcome data.[31]

Quantitative synthesis of data

Time to first flatus. A total of 686 patients were in the gum-chewing group and 688 in the control. The overall effect of the meta-analysis favored chewing gum, with a WMD of 0.31 days reduction (95% CI, –0.42 to –0.19; $P = 0.000$). However, it should be noted that nine trials have 95% CI crossing the zero level, and had a large heterogeneity for $I^2 = 73.5\%$; $P = 0.000$. (Fig. 3)

Table 1 Study characteristics of 17 randomized controlled trials on chewing gum following abdominal surgery

Study, year	Country	Type of surgery	Indication of surgery	Patient number/female		Mean age (year)		Mean duration of surgery (min)		Rate of complications		Time of chewing gum
				Gum	Control	Gum	Control	Gum	Control	Gum	Control	
Asao *et al.*, 2002[12]	Japan	Lapar	Colectomy	10/7	9/6	58.6	60.6	154	166	0/10	1/9	Tid
McCormick *et al.*, 2005[26]	US	Open& Lapar	Colectomy	53/NR	35/NR	NR	NR	NR	NR	NR	NR	Qid, for 15 min
Matros *et al.*, 2006[27]	US	Open	Colectomy	22/14	21/9	62.0	58.0	158	174	4/22	10/21	Tid, for 45 min
Schuster *et al.*, 2006[14]	US	Open	Colectomy	17/6	17/5	60.0	63.0	108	115	1/17	2/17	Tid, for 1 h
Chou *et al.*, 2006[29]	China	NS	Gastrectomy	13/7	13/8	50.1	51.9	271	286	1/13	0/13	Qid, for 5 min
Quah *et al.*, 2006[28]	UK	Open	Colectomy	19/6	19/7	67.0	68.0	155	150	5/19	6/19	Tid, for > 5 min
Hirayama *et al.*, 2006[13]	Japan	Open	Colectomy	10/5	14/6	55.6	60.6	251	193	3/10	5/14	Tid, for 30 min
Zhang and Zhao, 2008[16]	China	NS	Gastrointestinal surgery	9/2	9/2	8.6	7.4	115	123	0/9	0/9	Tid
Abd-El-Maeboud *et al.*, 2009[17]	Egypt	Open	Caesarean section.	93/93	107/107	26.2	26.4	41	38	15/93	43/107	Every 2 h, for 15 min
Cavusoglu *et al.*, 2009[30]	Turkey	Open	Intestinal resection	15/9	15/3	7.2	7.0	124	132	1/15	4/15	Tid, for 1 h
Crainic *et al.*, 2009[31]	US	Open & Lapar	Colectomy	20/NR	24/NR	NR	NR	NR	NR	NR	NR	Tid, for 30 min
Kafali *et al.*, 2010[18]	Turkey	Open	Caesarean section	74/74	76/76	29.3	29.2	32	31	NR	NR	Tid, for 1 h
Ngowe *et al.*, 2010[19]	Cameroon	Open	Appendectomy	23/10	23/10	42.4	43.7	113	109	3/23	2/23	Tid, for 30 min
Shang *et al.*, 2010[20]	China	Open	Caesarean section	195/195	191/191	29.4	29.9	34	35	23/195	41/191	Tid, for 1 h
Bahena-Aponte *et al.*, 2010[21]	Mexico	Open	Colectomy	16/5	16/7	55.6	56.6	NR	NR	2/16	0/16	Tid, for 30 min
Marwah *et al.*, 2012[24]	India	Open	Ileostomy	50/18	50/14	36.9	39.9	109	112	17/50	19/50	Tid, for 1 h
Ledari *et al.*, 2012[23]	Iran	Open	Caesarean section	50/50	50/50	27.9	28.5	33	31	0/50	0/50	Tid, for > 1 h

Lapar, laparoscopic; NR, not report; NS, not state; Qid, quarter in die; Tid, three time a day.

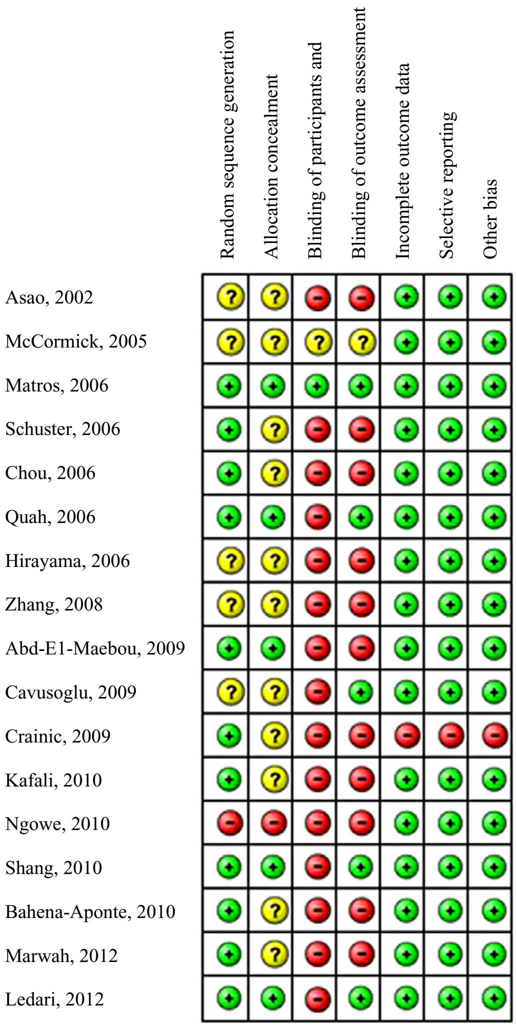

Figure 2 Risk of bias summary: Review authors' judgments about each risk of bias item across all included studies. (+) Low risk; (−) High risk; (?) Unclear risk.

Time to first bowel movement. A total of 573 patients were in the gum-chewing group and 567 in the control. The overall effect of the meta-analysis favored chewing gum, with a WMD of 0.51 days reduction (95% CI, −0.73 to −0.29; $P = 0.000$). However, seven trials had 95% CI crossing the zero level, and also had a large heterogeneity for $I^2 = 86.4\%$; $P = 0.000$. (Fig. 4)

LOS. A total of 600 patients were in the gum-chewing group and 592 in the control. The overall effect of the meta-analysis favored gum chewing, with a WMD of 0.72 days reduction (95% CI, −1.02 to −0.43; $P = 0.000$). However, 10 trials had 95% CI crossing the zero level, and also had a large heterogeneity for $I^2 = 87.2\%$; $P = 0.000$. (Fig. 5)

Complications. Postoperative complications were reported in all but two studies.[16,29] A summary of complications rate is shown in Table 1. It shows that gum chewing was associated with a lower incidence of postoperative complications. But complications were varied in each trail and not related to individual patients experiencing them; hence, statistical analysis of significance between these groups was not valid.

Sensitivity analysis. Firstly, subgroup analysis was performed to explore heterogeneity between studies and assess the robustness of our findings (Table 2). The studies that underwent colectomy yielded a WMD of 0.3 days reduction in time to flatus but without significance (95% CI, −0.68 to 0.08; $P = 0.119$); a significant reduction of 0.74 days in time to bowel movement (95% CI, −1.37 to −0.11; $P = 0.038$); a WMD of 1.10 days reduction in LOS but without significance (95% CI, −2.37 to 0.177; $P = 0.089$). All of them had a large heterogeneity with $I^2 = 73.5\%$, 86.4%, and 87.2%, respectively. Subgroup analysis for cesarean section demonstrated a significant decrease in all outcomes: time to flatus with WMD, −0.26 (95% CI −0.31 to −0.22; $P = 0.000$); time to bowel movement with WMD, −0.26 (95% CI −0.43 to −0.08; $P = 0.004$); LOS with WMD, −0.21 (95% CI −0.39 to −0.03; $P = 0.021$). All had a large heterogeneity except for time to flatus analysis ($I^2 = 1.0\%$, $I^2 = 85.8\%$, and $I^2 = 86.7\%$, respectively). Studies that underwent other abdominal surgery yielded a robust finding, associated with a significant reduction in all outcomes ($P = 0.000$) and demonstrated no heterogeneity ($I^2 < 60\%$, $P > 0.05$). Studies evaluating open surgery demonstrated similar results with the overall effect. However for the laparoscopic, results were completely opposite, with all outcomes having no significance.

Even though a subgroup analysis has been used, the heterogeneity of colectomy studies remained large. Sensitivity analyses were performed to examine whether the effect estimate was robust by sequential omission of individual studies using random-effects estimates. The colectomy studies, excluding one study[31] that reported 17 missing values and the duration time in treatment group longer than control, yielded opposite results in time to flatus (WMD, 0.49; 95% CI, −0.88 to −0.11; $P = 0.012$), but with substantial evidence of heterogeneity ($I^2 = 69.7\%$, $P = 0.002$). There was no change in time to bowel movement and LOS. In this base, excluding other two studies[12,13] in which patients were less than 30 yielded significant reduction of 0.24 days in time to flatus ($P = 0.049$), 0.69 days in time to bowel movement ($P = 0.000$), and demonstrated no heterogeneity ($I^2 = 0.0\%$ and $I^2 = 32.5\%$, respectively). However, there was 1.11 days reduction in LOS without statistical significance ($P = 0.106$), which also demonstrated large heterogeneity ($I^2 = 81.3\%$, $P = 0.000$). Further exclusion of other single studies did not materially alter the overall combined WMD. Sensitivity analysis was not performed on laparoscopic surgery for the small number of studies.

Publication bias. Publication bias was assessed by Begg's funnel plots and Egger's tests. The shapes of the Begg's funnel plots revealed no obvious asymmetry (Fig. 6). The Egger's test was then used to statistically assess funnel plot symmetry. The funnel plot was relatively symmetrical, suggesting that publication bias was not present. ($t = -0.38$, $P = 0.580$ for time to first flatus; $t = -1.05$, $P = 0.287$ for time to bowel movement; $t = -1.56$, $P = 0.078$ for LOS). These indicated that the results of these meta-analyses were relatively stable and that publication bias was unlikely to affect the results of the meta-analysis.

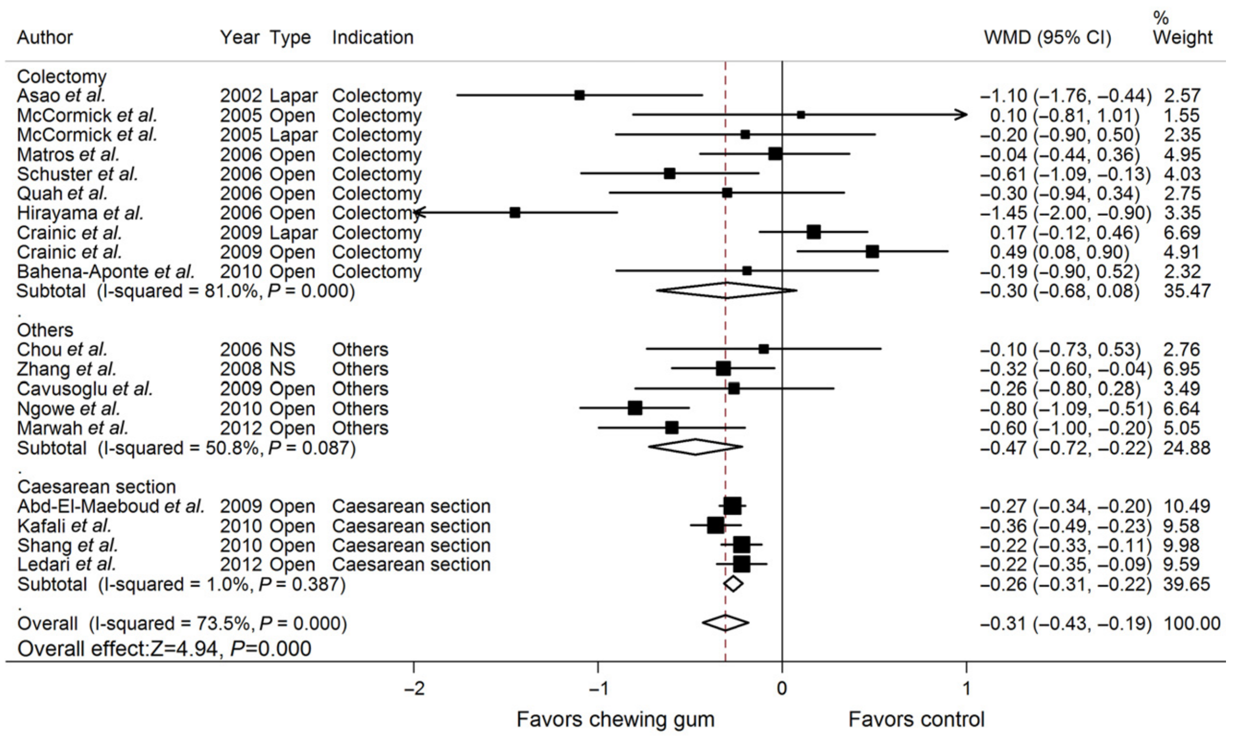

Figure 3 Overall and subgroup analysis of weighted mean difference (WMD) for time to first flatus (days) using random-effects model. CI, confidence interval.

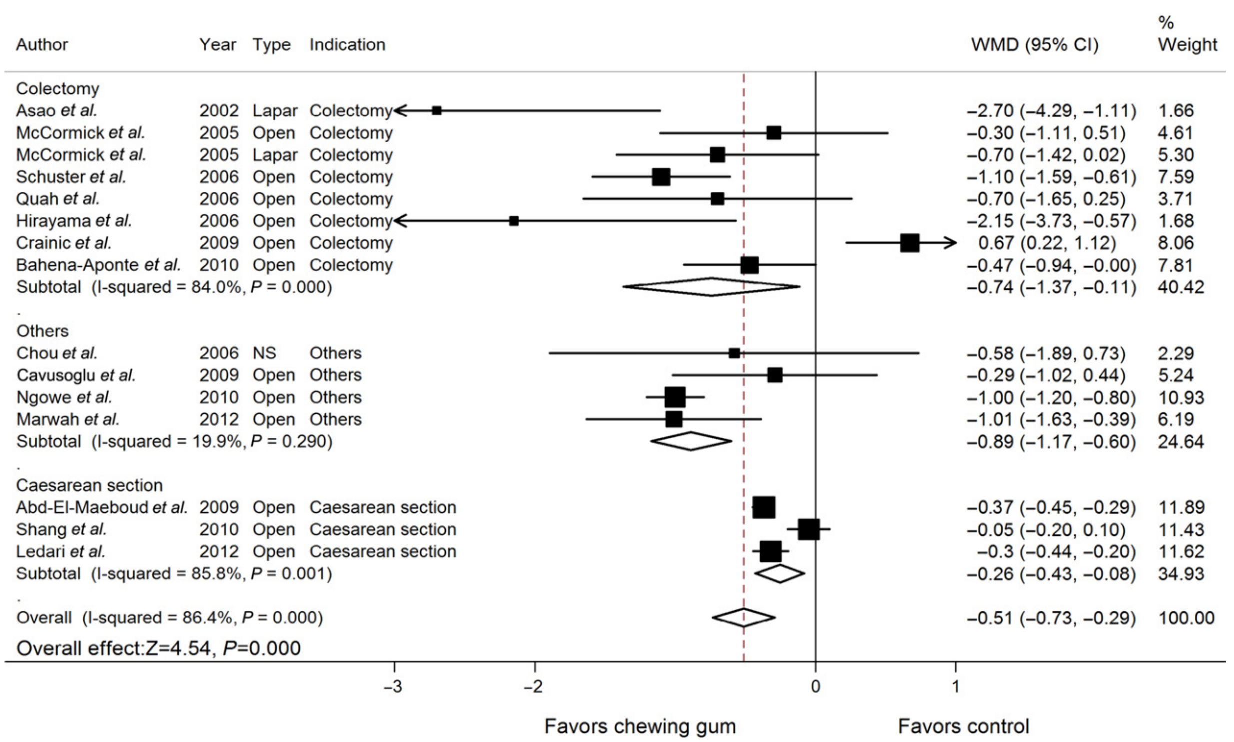

Figure 4 Overall and subgroup analysis of weighted mean difference (WMD) for time to first bowel movement (days) using random-effects model. CI, confidence interval.

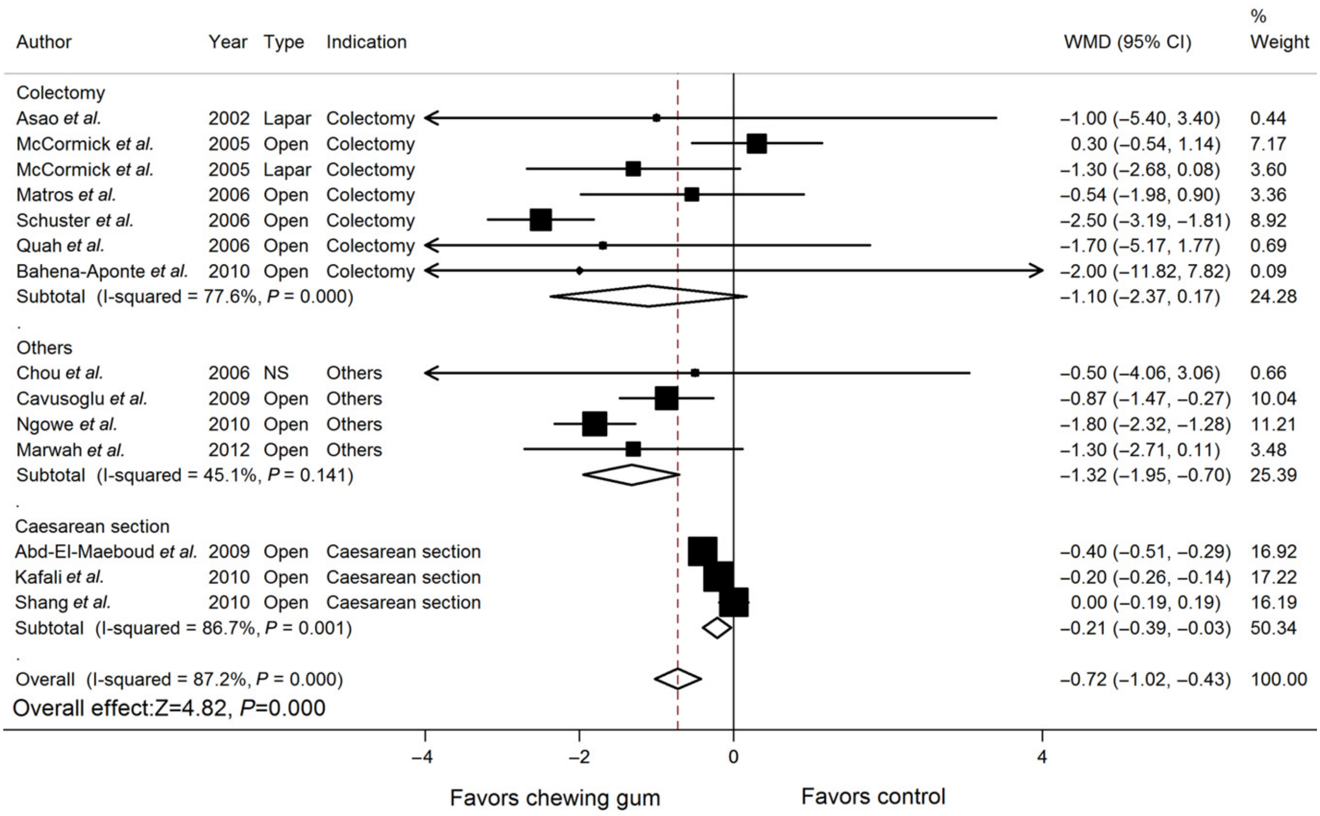

Figure 5 Overall and subgroup analysis of weighted mean difference (WMD) for time to length of hospital stay (days) using random-effects model. CI, confidence interval.

Cumulative meta-analysis. A statistically significant effect of chewing gum on abdominal surgery was first observed after publication of the first trial in 2002 (1.1 days reduction in time to flatus, $P < 0.01$; 2.7 days reduction in time to bowel movement, $P < 0.01$). Although subsequent trials had increased the precision of the point estimate, no substantive change had occurred in the direction or magnitude of the treatment effect. A statistically significant effect on time to first flatus of chewing gum following abdominal surgery was consistently observed after publication of the seventh trial in 2006, third trial in 2006 on time to bowel movement, and seventh trial in 2006 on LOS. (Fig. 7)

Discussion

At present, the association between chewing gum and POI is not fully understood. Increasing evidence that chewing gum reduces recovery time in abdominal surgical patients has been available for many years. The treatment effect varies somewhat according to the type of surgery and indication of surgery, but the effect is most accordance. It is well accepted that chewing gum as a type of sham feeding stimulates bowel motility.[10,11] However, whether chewing gum reduces POI remains controversial. This study systematically estimates the effects of chewing gum for postoperative treatment of ileus following abdominal surgery and conjectures the potential benefits of its use, if possible, providing an inexpensive, well-tolerated, and widely available solution to ameliorate an old problem. Our meta-analysis of 17 RCTs provides evidence that chewing gum significantly reduces recovery time following abdominal surgery. Patients in the chewing gum treatment group, compared with the reference group, experienced a significant reduction of 0.31 days for time to first flatus, 0.51 days for time to first bowel movement, 0.72 days for LOS (Figs 3–5).

Mechanisms of chewing gum reduce POI. The underlying mechanism involved in the association between chewing gum and POI is uncertain. One possible explanation is that chewing acts as sham feeding, stimulating the motility of human stomach,[48] duodenum,[11] and rectum.[10] Another explanation is chewing may trigger the release of gastrointestinal hormones[49] and increase the secretion of saliva and pancreatic juice, gastrin, and neurotensin.[48] Thus, it seems that the mechanisms are multimodal. However, for an intervention that is so cheap, effective, well tolerated, and free of side effects, it may be used clinically even before knowing the mechanism behind its success and important health and economic benefits.

Sources of heterogeneity. Heterogeneity is a potential problem that may affect the interpretation of the results. The present meta-analysis showed that there was large heterogeneity

Table 2 Subgroup analysis based on 17 randomized controlled trials of chewing gum after abdominal surgery

Outcome	No. of Patients	No. of Studies	WMD (95% CI)	*P*-value	Heterogeneity	
					I^2 (%)	*P*
Overall effect						
Time to first flatus	1374	17	–0.31 (–0.43, –0.19)	0.000	73.5	0.000
Time to first bowel movement	1140	14	–0.51 (–0.73, –0.29)	0.000	86.4	0.000
Length of hospital stay	1192	13	–0.72 (–1.02, –0.43)	0.000	87.2	0.000
Indication of surgery: colectomy						
Time to first flatus	318	8	–0.30 (–0.68, 0.08)	0.119	81.0	0.000
Time to first bowel movement	252	7	–0.74 (–1.37, –0.11)	0.038	84.0	0.000
Length of hospital stay	254	6	–1.10 (–2.37, 0.177)	0.089	77.6	0.000
Indication of surgery: caesarean section						
Time to first flatus	836	4	–0.26 (–0.31, –0.22)	0.000	1.0	0.387
Time to first bowel movement	388	3	–0.26 (–0.43, –0.08)	0.004	85.8	0.000
Length of hospital stay	736	3	–0.21 (–0.39, –0.03)	0.021	86.7	0.001
Indication of surgery: others						
Time to first flatus	220	5	–0.47 (–0.72, –0.22)	0.000	50.8	0.087
Time to first bowel movement	202	4	–0.89 (–1.17, –0.60)	0.000	19.9	0.290
Length of hospital stay	202	4	–1.32 (–1.95, –0.70)	0.000	45.1	0.141
Studies of open surgery†						
Time to first flatus	1237	14	–0.33 (–0.46, –0.20)	0.000	75.3	0.000
Time to first bowel movement	1044	12	–0.46 (–0.68, –0.23)	0.000	88.3	0.000
Length of hospital stay	1093	11	–0.70 (–1.01, –0.40)	0.000	89.9	0.000
Studies of laparoscopic surgery†						
Time to first flatus	93	3	–0.34 (–1.11, 0.43)	0.388	83.3	0.003
Time to first bowel movement	70	2	–1.57 (–3.51, 0.37)	0.114	80.2	0.025
Length of hospital stay	70	2	–1.27 (–2.59, 0.05)	0.058	0.0	0.898

†Studies that underwent both open and laparoscopic surgeries were analyzed separately.
CI, confidence interval; WMD, weighted mean difference.

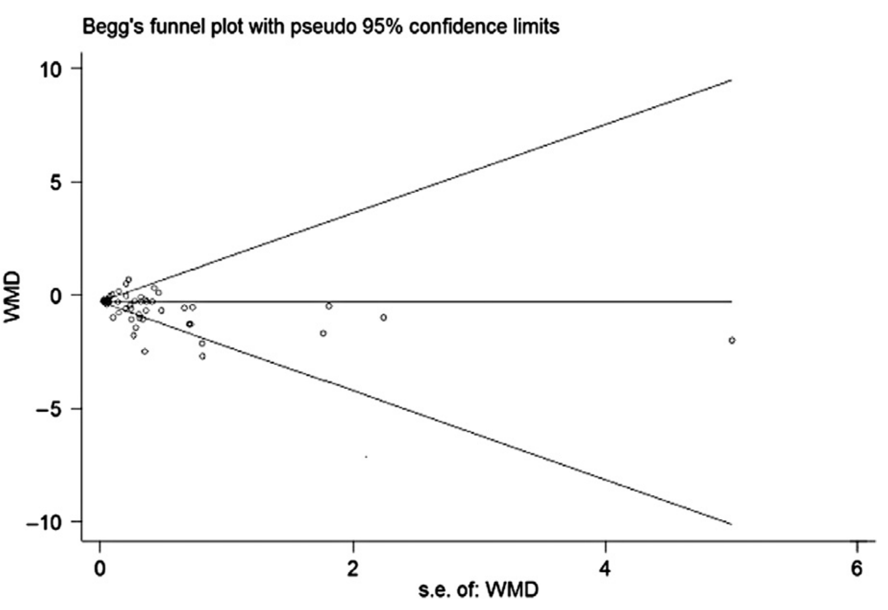

Figure 6 Funnel plots for publication bias in the studies of the meta-analysis of chewing gum following abdominal surgery. s.e., standard error; WMD, weighted mean difference.

between studies (Table 2). Subsequent subgroup analysis stratified by indication of surgery, type of surgery, and quality of study identified large heterogeneity mostly as well, indicating that indication of surgery, type of surgery, and quality of study contributed little to the existence of overall heterogeneity. We performed sensitivity analysis on these subgroup analyses. On the colectomy subgroup, the studies by Crainic *et al*.[31] had longer duration time in the treatment group than the control and had 17 missing values

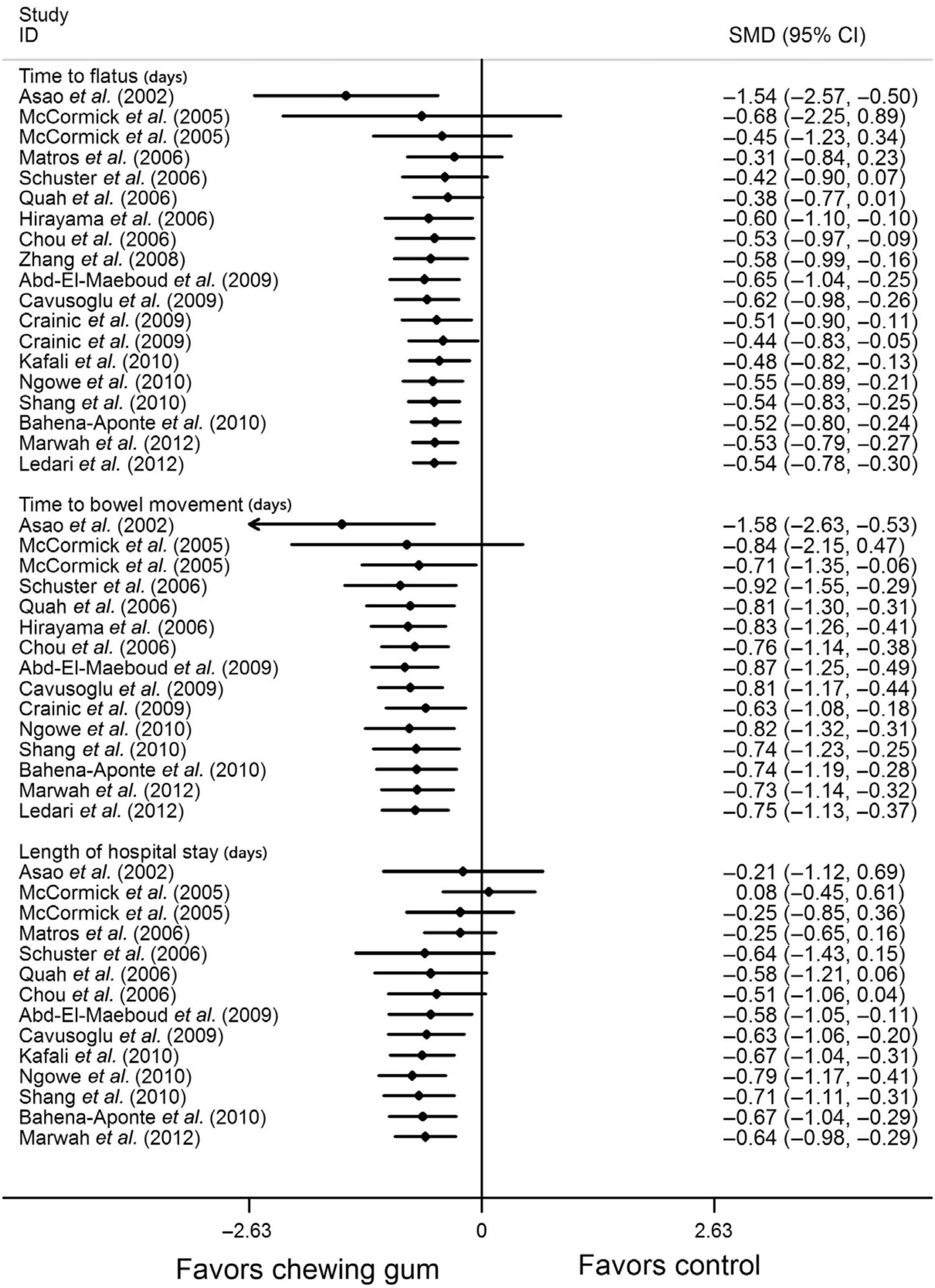

Figure 7 Cumulative meta-analysis of 17 randomized controlled trials on the efficacy of chewing gum following abdominal surgery. CI, confidence interval; SMD, standard mean difference.

in the results. Dropping this study yielded opposite results in time to flatus, with a statistical significance of 0.49 days shorten ($P = 0.012$), but also with a large heterogeneity ($I^2 = 69.7\%$). Sensitivity analysis showed that the study by Asao *et al.*,[12] Hirayama *et al.*,[13] and Crainic *et al.*[31] had a large impact on our results. The study patients in their report were less than 30. Dropping these three studies from our analysis did increase the benefit seen from chewing gum with regard to time to first flatus and time to first bowel movement, but had no significance on LOS.

Twelve trials underwent open surgery, one underwent laparoscopic surgery,[12] and two underwent both.[26,31] The results for the cohorts were analyzed separately on subgroup analysis. But on the laparoscopic surgery studies, only two of them[12,26] reported time to first bowel movement and LOS as outcomes. Although a trend toward shorter duration of time to flatus, first bowel movement and LOS in patients who underwent laparoscopic surgery, none of the results were significant. Laparoscopic surgery is known to reduce the inflammatory response, and in so doing, promotes a faster recovery.[50] Many studies suggest a significant reduction in LOS on laparoscopic surgery compared with the open technique.[51,52] The explanations of incongruent results in our subgroup analysis may be owing to: (i) the small number of cases and participants of the three trials increased the possibility that chance accounted for their results; (ii) the study by Crainic *et al.*[31] reported both open and laparoscopic procedure results, having incomplete data and even with longer duration time in treatment group longer than control; (iii) the study by Asao *et al.*[12] had relatively longer hospital stays than other studies (mean 13.5 days for gum-chewing group, 14.5 days for the control group). It is worth mentioning that no definitions of discharge criteria were given in any of the studies to help interpret LOS outcomes. These may explain the large heterogeneity between laparoscopic surgery studies in some degree. Therefore, considerably larger and more rigorous studies are needed to determine the effect of chewing gum on duration of postoperative hospital stay after laparoscopic surgery.

Study strengths and limitations. A major strength of our study is that all the included original studies used an RCT design, which has well comparability of the two groups and minimizes selection bias. Moreover, we included all abdominal surgery and then performed subgroup analysis based on different indication of surgery. There is sufficient evidence of 17 RCTs to conclude that chewing gum shortens time of outcomes in patients undergoing abdominal surgery. Although some studies had conducted a meta-analysis of relation between chewing gum and POI and demonstrated a significant effect, all were only about one surgery indication.[34–37] With the accumulating evidence and enlarged sample size, we have enhanced statistical power to provide more precise and reliable efficiency estimates. We have shown that despite variation in results from each study, overall, the published evidence supports the hypothesis that gum chewing reduces the duration of POI. In addition, no publication bias was detected in this meta-analysis, which indicated that the pooled results of our study should be reliable.

One potential limitation of the present meta-analysis was that only one study included a double placebo group to assess the treatment effect,[27] but because of their differing method of reporting results, not all of their data could be included in our analysis. Another study by Choi *et al.*[22] was excluded because of insufficient data that rendered the meta-analysis impossible. The study by Choi *et al.*[22] underwent open and laparoscopic cystectomy for bladder cancer surgery and found a significant time for the amelioration of ileus. A second limitation is the lack of blinding in most studies, leading to potential bias by the investigator recording the results. Double blinding should be difficult in this project, but blinding the observer is achievable and would reduce bias of the results. A third limitation is the substantial heterogeneity among studies. Despite assessing outcomes only in patients undergoing colectomy, it also identified large heterogeneity. Nevertheless, we were able to detect the major source of heterogeneity through the sensitivity analyses. In other hand, residual confounding is of concern. Uncontrolled or unmeasured confounding factors such as opioids, epidural analgesia, and early enteral feeding etc. potentially produce biases. Unfortunately, several studies did not state postoperative practice in this respect. Furthermore, because current data in efficacy of chewing gum after laparoscopic surgery are sparse, we were unable to assess consistent results for these outcomes. New trials with better design are necessary for patients who undergo laparoscopic surgery before gum chewing becomes a routine feature of the postoperative management.

Conclusions

In conclusion, the current evidence suggests that gum chewing following abdominal surgery offers significant benefits in reducing the time to resolution of POI and LOS. However, for the subgroup of colectomy and laparoscopic surgery, inconsistent results were presented. Well-designed, large-scale, blinded, randomized, controlled trials with a placebo arm studies were urgently needed to answer the question of whether gum chewing can significantly reduce POI in different abdominal surgeries.

Acknowledgment

This work was not supported by any kind of fund.

References

1 Mattei P, Rombeau JL. Review of the pathophysiology and management of postoperative ileus. *World J. Surg.* 2006; **30**: 1382–91.
2 Maron DJ, Fry RD. New therapies in the treatment of postoperative ileus after gastrointestinal surgery. *Am. J. Ther.* 2008; **15**: 59–65.
3 Behm B, Stollman N. Postoperative ileus: etiologies and interventions. *Clin. Gastroenterol. Hepatol.* 2003; **1**: 71–80.
4 Delaney CP. Clinical perspective on postoperative ileus and the effect of opiates. *Neurogastroenterol. Motil.* 2004; **16** (Suppl. 2): 61–6.
5 Holte K, Kehlet H. Postoperative ileus: a preventable event. *Br. J. Surg.* 2000; **87**: 1480–93.
6 Kehlet H, Holte K. Review of postoperative ileus. *Am. J. Surg.* 2001; **182**: 3S–10S.
7 Doorly MG, Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. *Surg. Clin. North Am.* 2012; **92**: 259–72, viii.
8 Marderstein EL, Delaney CP. Management of postoperative ileus: focus on alvimopan. *Ther. Clin. Risk Manag.* 2008; **4**: 965–73.

9 Vermeulen H, Storm-Versloot MN, Busch OR, Ubbink DT. Nasogastric intubation after abdominal surgery: a meta-analysis of recent literature. *Arch. Surg.* 2006; **141**: 307–14.
10 Jepsen JM, Skoubo-Kristensen E, Elsborg L. Rectosigmoid motility response to sham feeding in irritable bowel syndrome. Evidence of a cephalic phase. *Scand. J. Gastroenterol.* 1989; **24**: 53–6.
11 Soffer EE, Adrian TE. Effect of meal composition and sham feeding on duodenojejunal motility in humans. *Dig. Dis. Sci.* 1992; **37**: 1009–14.
12 Asao T, Kuwano H, Nakamura J, Morinaga N, Hirayama I, Ide M. Gum chewing enhances early recovery from postoperative ileus after laparoscopic colectomy. *J. Am. Coll. Surg.* 2002; **195**: 30–2.
13 Hirayama I, Suzuki M, Ide M, Asao T, Kuwano H. Gum-chewing stimulates bowel motility after surgery for colorectal cancer. *Hepatogastroenterology* 2006; **53**: 206–8.
14 Schuster R, Grewal N, Greaney GC, Waxman K. Gum chewing reduces ileus after elective open sigmoid colectomy. *Arch. Surg.* 2006; **141**: 174–6.
15 Kouba EJ, Wallen EM, Pruthi RS. Gum chewing stimulates bowel motility in patients undergoing radical cystectomy with urinary diversion. *Urology* 2007; **70**: 1053–6.
16 Zhang Q, Zhao P. Influence of gum chewing on return of gastrointestinal function after gastric abdominal surgery in children. *Eur. J. Pediatr. Surg.* 2008; **18**: 44–6.
17 Abd-El-Maeboud KH, Ibrahim MI, Shalaby DA, Fikry MF. Gum chewing stimulates early return of bowel motility after caesarean section. *BJOG* 2009; **116**: 1334–9.
18 Kafali H, Duvan CI, Gozdemir E, Simavli S, Onaran Y, Keskin E. Influence of gum chewing on postoperative bowel activity after cesarean section. *Gynecol. Obstet. Invest.* 2010; **69**: 84–7.
19 Ngowe MN, Eyenga VC, Kengne BH, Bahebeck J, Sosso AM. Chewing gum reduces postoperative ileus after open appendectomy. *Acta Chir. Belg.* 2010; **110**: 195–9.
20 Shang H, Yang Y, Tong X, Zhang L, Fang A, Hong L. Gum chewing slightly enhances early recovery from postoperative ileus after cesarean section: results of a prospective, randomized, controlled trial. *Am. J. Perinatol.* 2010; **27**: 387–91.
21 Bahena-Aponte JA, Cardenas-Lailson E, Chavez-Tapia N, Flores-Gama F. Usefulness of chewing gum for the resolution of postoperative ileus in left colon resections. *Rev. Gastroenterol. Mex.* 2010; **75**: 369–73.
22 Choi H, Kang SH, Yoon DK *et al*. Chewing gum has a stimulatory effect on bowel motility in patients after open or robotic radical cystectomy for bladder cancer: a prospective randomized comparative study. *Urology* 2011; **77**: 884–90.
23 Ledari FM, Barat S, Delavar MA. Chewing gums has stimulatory effects on bowel function in patients undergoing cesarean section: a randomized controlled trial. *Bosn. J. Basic Med. Sci.* 2012; **12**: 265–8.
24 Marwah S, Singla S, Tinna P. Role of gum chewing on the duration of postoperative ileus following ileostomy closure done for typhoid ileal perforation: a prospective randomized trial. Saudi. *J. Gastroenterol.* 2012; **18**: 111–17.
25 Takagi K, Teshima H, Arinaga K *et al*. Gum chewing enhances early recovery of bowel function following transperitoneal abdominal aortic surgery. *Surg. Today* 2012; **42**: 759–64.
26 McCormick J, Garvin R, Caushaj P. The effects of gum-chewing on bowel function and hospital stay after laparoscopic vs open colectomy: a multi-institution prospective randomized trial. *J. Am. Coll. Surg.* 2005; **201**: S66–S7.
27 Matros E, Rocha F, Zinner M *et al*. Does gum chewing ameliorate postoperative ileus? Results of a prospective, randomized, placebo-controlled trial. *J. Am. Coll. Surg.* 2006; **202**: 773–8.
28 Quah HM, Samad A, Neathey AJ, Hay DJ, Maw A. Does gum chewing reduce postoperative ileus following open colectomy for left-sided colon and rectal cancer? A prospective randomized controlled trial. *Colorectal Dis.* 2006; **8**: 64–70.
29 Chou SJ, Lin CH, Hsieh HF, Yu JC, Chen TW, Chan DC. Gum chewing in patients with subtotal gastrectomy. *Chir. Gastroenterol.* 2006; **22**: 269–71.
30 Cavusoglu YH, Azili MN, Karaman A *et al*. Does gum chewing reduce postoperative ileus after intestinal resection in children? A prospective randomized controlled trial. *Eur. J. Pediatr. Surg.* 2009; **19**: 171–3.
31 Crainic C, Erickson K, Gardner J *et al*. Comparison of methods to facilitate postoperative bowel function. *Medsurg Nurs.* 2009; **18**: 235–8.
32 Smith SR, Lim P, Draganic B. Effect of gum chewing on gastrointestinal recovery after laparoscopic colorectal resectional surgery: a prospective randomized clinical trial [Abstract]. *ANZ J. Surg.* 2010; **80** (Suppl.): A17.
33 Chan MK, Law WL. Use of chewing gum in reducing postoperative ileus after elective colorectal resection: a systematic review. *Dis. Colon Rectum* 2007; **50**: 2149–57.
34 de Castro SM, van den Esschert JW, van Heek NT *et al*. A systematic review of the efficacy of gum chewing for the amelioration of postoperative ileus. *Dig. Surg.* 2008; **25**: 39–45.
35 Purkayastha S, Tilney HS, Darzi AW, Tekkis PP. Meta-analysis of randomized studies evaluating chewing gum to enhance postoperative recovery following colectomy. *Arch. Surg.* 2008; **143**: 788–93.
36 Noble EJ, Harris R, Hosie KB, Thomas S, Lewis SJ. Gum chewing reduces postoperative ileus? A systematic review and meta-analysis. *Int. J. Surg.* 2009; **7**: 100–5.
37 Fitzgerald JE, Ahmed I. Systematic review and meta-analysis of chewing-gum therapy in the reduction of postoperative paralytic ileus following gastrointestinal surgery. *World J. Surg.* 2009; **33**: 2557–66.
38 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; **354**: 1896–900.
39 Higgins JP, Altman DG, Gotzsche PC *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
40 Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001; **323**: 157–62.
41 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 2002; **21**: 1539–58.
42 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.
43 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control. Clin. Trials* 1986; **7**: 177–88.
44 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl Cancer Inst.* 1959; **22**: 719–48.
45 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088–101.
46 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.
47 Watson H, Griffiths P, Lamparelli M, Watson M. Does chewing (gum) aid recovery after bowel resection? A randomized controlled trial (RCT). *Colorectal Dis.* 2008; **10**: 6.

48 Stern RM, Crawford HE, Stewart WR, Vasey MW, Koch KL. Sham feeding. Cephalic-vagal influences on gastric myoelectric activity. *Dig. Dis. Sci.* 1989; **34**: 521–7.
49 Kellow JE, Delvaux M, Azpiroz F, Camilleri M, Quigley EM, Thompson DG. Principles of applied neurogastroenterology: physiology/motility-sensation. *Gut* 1999; **45** (Suppl. 2): II17–24.
50 Chen HH, Wexner SD, Iroatulam AJ *et al*. Laparoscopic colectomy compares favorably with colectomy by laparotomy for reduction of postoperative ileus. *Dis. Colon Rectum* 2000; **43**: 61–5.
51 Burgdorf SK, Rosenberg J. Short hospital stay after laparoscopic colorectal surgery without fast track. *Minim. Invasive Surg.* 2012; **2012**: 260–73.
52 Li MZ, Xiao LB, Wu WH, Yang SB, Li SZ. Meta-analysis of laparoscopic versus open colorectal surgery within fast-track perioperative care. *Dis. Colon Rectum* 2012; **55**: 821–7.