World J Surg (2009) 33:2557–2566
DOI 10.1007/s00268-009-0104-5

Systematic Review and Meta-Analysis of Chewing-Gum Therapy in the Reduction of Postoperative Paralytic Ileus Following Gastrointestinal Surgery

J. Edward F. Fitzgerald · Irfan Ahmed

Published online: 10 September 2009

Abstract

Background Postoperative ileus has long been considered an inevitable consequence of gastrointestinal surgery. It prolongs hospital stay, increases morbidity, and adds to treatment costs. Chewing is a form of sham feeding reported to stimulate bowel motility. This analysis examines the value of chewing-gum therapy in treatment of postoperative ileus.

Methods A search for randomized, controlled trials studying elective gastrointestinal surgery was undertaken using MEDLINE, Embase, Cochrane Controlled Trials Register, and reference lists. Outcomes were extracted including time to first flatus and bowel motion, length of stay, and complications. Statistical analysis was undertaken using the weighted mean difference (WMD) and random-effects model with 95% confidence intervals (CI).

Results Seven studies with 272 patients were included. For time to first flatus the analysis favored treatment with a WMD of 12.6 h (17%) reduction (95% CI −21.49 to −3.72; $P = 0.005$). For time to first bowel motion, treatment was favored with a WMD of 23.11 h (22%) reduction (95% CI −34.32 to −11.91; $P < 0.001$). For length of stay, the analysis showed a nonsignificant trend toward treatment with WMD of 23.88 h (12%) reduction (95% CI −53.29 to +5.53; $P = 0.11$). There were no significant differences in complication rates.

Conclusions Chewing-gum therapy following open gastrointestinal surgery is beneficial in reducing the period of postoperative ileus, although without a significant reduction in length of hospital stay. These outcomes are not significant for laparoscopic gastrointestinal surgery.

Electronic supplementary material The online version of this article (doi:10.1007/s00268-009-0104-5) contains supplementary material, which is available to authorized users.

J. E. F. Fitzgerald (✉)
Department of Gastrointestinal Surgery, Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, UK
e-mail: edwardfitzgerald@doctors.org.uk

I. Ahmed
Department of Surgery, Aberdeen Royal Infirmary, Aberdeen AB25 2ZA, Scotland

Present Address:
J. E. F. Fitzgerald
Medical Education Unit, University of Nottingham Medical School, Queens Medical Centre, Derby Road, Nottingham NG7 2UH, UK

Introduction

Postoperative ileus has long been considered an inevitable consequence of abdominal surgery. It has been defined as "transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of intake" [1]. To the patient, this translates as delayed recovery and prolonged hospital stay. Symptoms are characterized by nausea, vomiting, abdominal distension, pain, inability to tolerate an oral diet, and a delay in the return of normal gastrointestinal function with the passage of flatus and stool.

In addition to increased patient morbidity, the economic burden of this lengthened hospital stay is substantial. In one review of patients undergoing hemicolectomy, prolonged postoperative ileus increased the duration of hospitalization by an average of 8 days with additional median costs of $14,904 [2]. Previous studies estimated overall annual health care expenditure in relation to postoperative ileus at between $750 million and $1 billion in the United States

[3]. Despite this, research has shown wide variations between surgeons with regard to awareness, recognition, and management of this condition [4].

The treatment of postoperative ileus has traditionally been supportive, with nasogastric decompression, intravenous fluids, and watchful waiting. However, the widespread introduction of enhanced patient recovery protocols has driven new research in this area, focusing on mechanisms and treatments for this major cause of delayed discharge.

Although the etiology of postoperative ileus is not fully understood, research has suggested numerous contributing factors, including pharmacologic (e.g., general anesthetic and opioid analgesia), inflammatory causes (e.g., bowel manipulation and inflammatory mediator release), and neural reflexes (postoperative sympathetic overactivity or other inhibitory neuronal pathways) [5, 6]. It seems likely that the etiology is multifactorial and varies according to the original insult, as evidenced by the varying success of treatments specifically targeting these individual causes.

One of these treatments is based on the physiologic theory of "sham feeding." Cephalic-vagal stimulation from chewing alone gives rise to propulsive and hormonal gastrointestinal activity similar to that seen with normal eating [7]. Although early enteral feeding has also been shown to be beneficial, the effect on postoperative ileus varies and patient intolerance is high, especially following gastrointestinal surgery [8–10]. Several studies have tested the sham feeding hypothesis by using chewing-gum during the early postoperative period [11–18]. It has the advantage of being inexpensive, well tolerated, and widely available.

The objective of this review was to identify clinical trials of chewing-gum therapy in relation to postoperative ileus and analyze results by meta-analysis to show what benefit, if any, this may bring in providing a simple solution to ameliorate an old problem.

Methods

Methodology for the meta-analysis was undertaken in accordance with the proposals outlined in the QUOROM statement [19] and the Cochrane Handbook for Systematic Reviews of Intervention [20].

Identification of trials

A search using MEDLINE, Embase, and the Cochrane Controlled Trials Register were undertaken using the terms "ileus," "gum," "chewing," "motility," and "recovery" both alone and in combinations. No year limits or language restrictions were applied. To ensure all relevant articles were reviewed, the reference lists of the articles identified in this search were also included.

Study selection

Eligible trials were those in which adult patients had undergone elective open or laparoscopic gastrointestinal surgery for any indication. The intervention was postoperative gum-chewing versus no additional treatment (routine postoperative care). Only trials using a randomized, controlled methodology were included. Demographics, pre- and postoperative protocols, and the nature of the operations were recorded. Primary and secondary endpoints were identified, including time to first flatus, time to first bowel opening, length of hospital stay, and 30-day postoperative complications. Predefined exclusion criteria included poor methodology such that a study could not be adequately compared or where data was presented in a format that rendered meta-analysis impossible (once attempts to obtain raw data from the authors failed).

Validity assessment

Both authors scored papers on methodological quality using the five-point Jadad scale [21]. Assessment was blind to both authors and institution. There was no disagreement on scoring.

Data abstraction and study characteristics

Data were checked in duplicate by both authors using a standard form. The study method and outcomes were tabulated for comparison.

Data analysis

Time to first flatus, time to first bowel movement, length of stay, and complications were identified as continuous variables. Statistical analysis of the combined results was undertaken with a standard meta-analysis software package (Review Manager 4.2; Nordic Cochrane Centre, Cochrane Collaboration, Oxford, UK, 2003). The weighted mean difference (WMD) and random-effects model were used owing to the heterogeneity of the clinical trials examined. Data outcomes were presented with 95% confidence intervals (CI).

Results

Trial characteristics

We identified 10 trials that had investigated the effects of chewing-gum on postoperative ileus, and all were retrieved for further detailed evaluation. One sequential case series investigating the effect of gum chewing in patients undergoing urologic ileal conduit surgery was immediately excluded owing to nonrandomized methodology [22]. One study investigating undefined gastrointestinal surgery solely on children was also excluded [23]. Of those remaining, all were randomized, controlled trials with variable attempts at blinding. All studies stated the demographic attributes of enrolled patients, and they were broadly comparable. One study examined recovery following subtotal gastrectomy [11], with the remainder in the setting of colonic surgery. One study did not publish associated standard deviations alongside the relevant results and was subsequently excluded as we were unable to obtain this data from the authors [16]. One study published median endpoints rather than the mean [13]; the authors were subsequently able to provide appropriate data for time to first flatus and length of stay but not for time to first bowel motion.

The seven analyzed studies consisted of six published articles [11–15, 18] and one abstract [17]. A total of 272 patients were enrolled; they were a mix of patients undergoing surgery for benign and elective conditions. Operations were performed via open surgery [12–15], laparoscopic techniques [18], or both [17]. One study presented results for open and laparoscopic trial arms separately [17], and so these were analyzed in the meta-analysis as separate groups. One study did not clearly state whether patients underwent open or laparoscopic surgery [11].

All seven eligible studies included time to first flatus and time to first bowel motion as primary outcomes. All but one trial documented the length of stay [15]. There was variation in the units of reporting, with three studies recording outcomes in hours and three in days. All were converted to hours to allow uniform analysis.

Postoperative protocols differed among the studies. Of the included studies, three specified the make of gum used [12, 15, 18] and two listed nutritional ingredients without specifying the commercial brand [11, 13]. Gum chewing was uniformly commenced on postoperative day 1. Both daily duration and frequency of chewing were documented in five studies [11–13, 15, 17], varying between 5 and 30 min chewing three or four times a day. Two studies stated only frequency, not duration [14, 18]. Postoperative feeding regimens varied among studies. One study favored traditional "sips" until passage of first flatus [13]; the others did not state the protocol. For colonic surgery, only one study stated whether bowel preparation had been used prior to colonic surgery [12]. Three studies stated the protocol for postoperative analgesia [11–13]; two did not mention it specifically [15, 18], and one study stated "standard operating consultant preference" [14].

Trial flow

Trial methodology

Three trials clearly stated their methodology for randomization: sealed envelope [12], randomized card-pull design [11, 14], or computer-generated randomization, respectively [13]. One article described attempts at blinding and was also the only study to include a placebo group [13].

Outcomes

All studies included in the analysis measured time to *passage of first flatus* as an outcome (Fig. 1). A total of 144 patients were in the treatment group and 128 in the control. The test for overall effect favored treatment, with a WMD of 12.6 h reduction (95% CI −21.49 to −3.72; $P = 0.005$) in time to flatus. This represents a 17% reduction in comparison to the control group. However, it should be noted that five of the trial groups have 95% CI crossing the zero level.

All but one study [15] measured time to *first bowel motion* as an outcome. One study did not provide sufficient data for inclusion [13]. Of the remaining, 122 patients were enrolled in a treatment group and 107 in a control group. The results are shown in Fig. 2. The test for overall effect favored treatment, with a WMD of 23.11 h reduction in time to bowel opening (95% CI −34.32 to −11.91; $P < 0.0001$). This represents a 22% reduction in comparison to the control group. However, four of the trial groups had 95% confidence intervals crossing the zero level.

All but one study [15] included *length of stay* as an outcome. The results are shown in Fig. 3. A total of 134 patients were enrolled in the treatment group and 114 in the control group. The test for overall effect showed a non-statistically significant trend toward treatment, with a WMD of 23.88 h reduction in time to bowel opening (95% CI −53.29 to +5.53; $P = 0.11$). This represents a 12% reduction in comparison to the control group. However, six of the trial groups have 95% confidence intervals crossing the zero level.

All but two studies [11, 17] included 30-day postoperative *complications* as an outcome. A summary is shown in Table 1. Complications were counted separately and not related to individual patients experiencing them. As such, statistical analysis of significance between these groups is not valid.

Subgroup analysis

Given the variation in surgical interventions used in these randomized controlled trials, the meta-analysis was repeated omitting the small number of studies that utilized

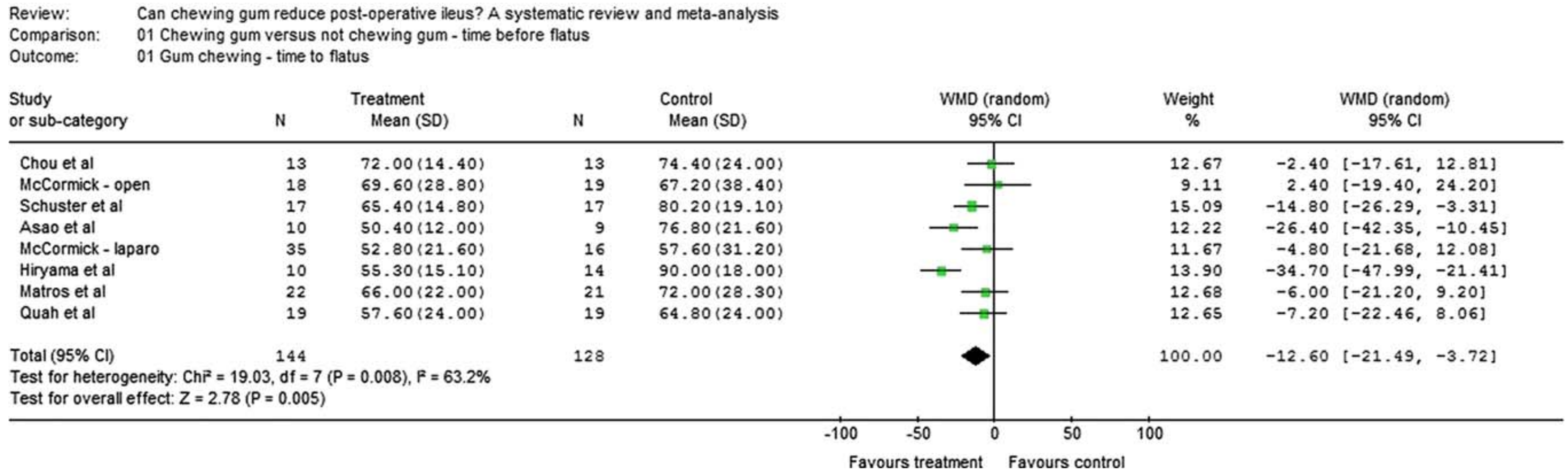

Fig. 1 Forrest plot of time to first flatus

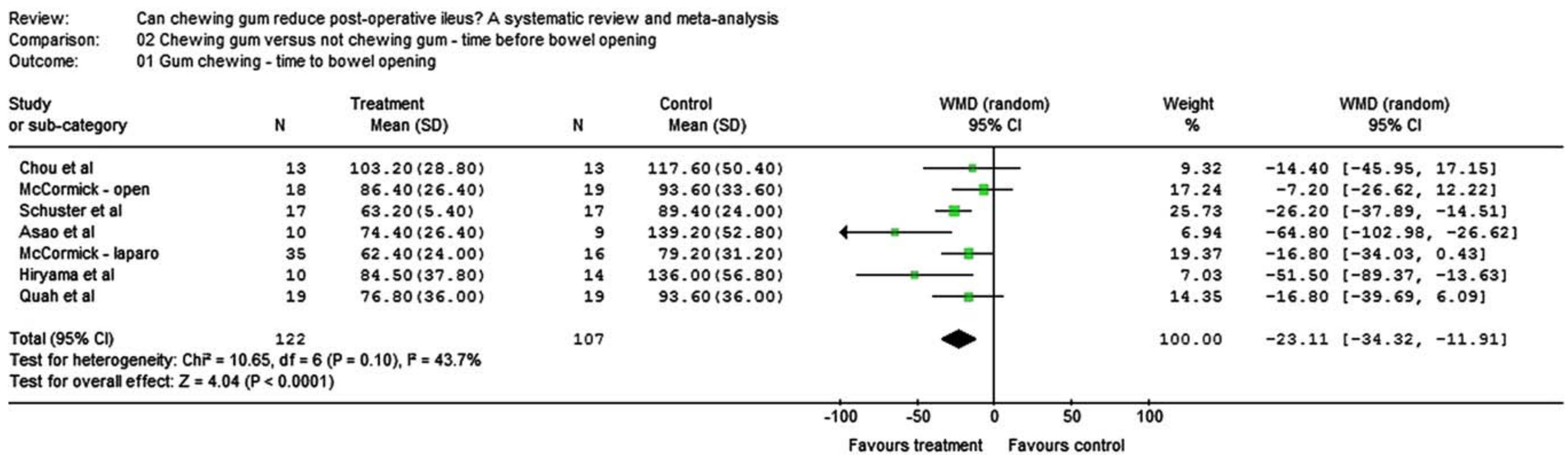

Fig. 2 Forrest plot of time to first bowel motion

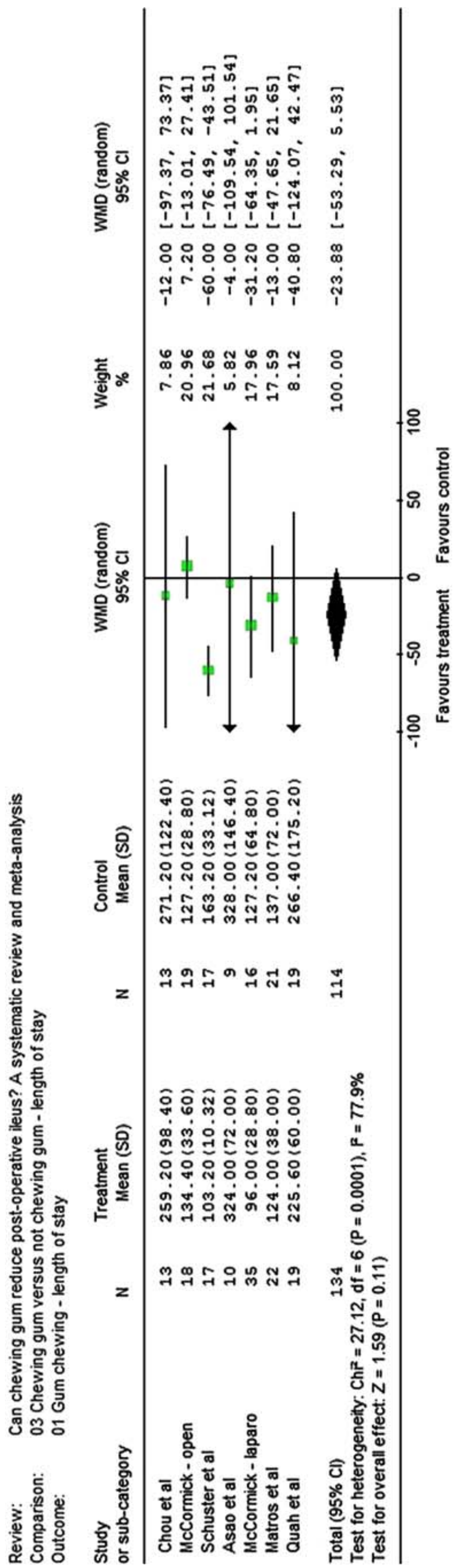

Fig. 3 Forrest plot of length of stay

laparoscopic surgery or did not specify [11, 18]. One study reported these results separately, enabling only the open surgery outcomes to be included [17]. The meta-analysis findings based purely on outcomes from open and laparoscopic surgery are shown in Table 2. There was no statistically significant difference between them (chi-squared test, $P = 0.192$).

Statistical notes

Further analysis of these findings based on all included studies with a fixed effect model did not materially change the outcomes of this analysis for time to first flatus or bowel motion. As such, the fixed effect model was used to examine these studies for publication bias with a funnel plot (Figs. 4, 5). This has suggested the possibility of a publication bias toward a positive effect. However, this must be set against the heterogeneity of the clinical trials examined. Egger's linear regression test was not used owing to the small number of studies in this analysis.

Discussion

This study systematically reviewed the effects of gum-chewing for postoperative treatment of ileus following gastrointestinal surgery and highlights the potential benefits of its use. It confirmed the findings of previous smaller published meta-analyses [24, 25], and for the first time the larger pooled results allow a detailed subgroup analysis of comparative outcomes based on surgical modality.

For more than a century this condition has challenged both patients and surgeons. The clinical and economic burden is substantial, encompassing delayed discharge, increased bed occupation, prolonged nursing time, and decreased patient satisfaction [26].

Current research theories regarding the etiology of postoperative ileus describe a biphasic pathologic reaction in the affected bowel. Initial mechanical factors, such as operative handling, result in activation of neural reflexes suppressing bowel motility via the sympathetic adrenergic pathway [27] and stimulating release of corticotropin-releasing factor [28]. These effects last a number of hours, after which a second inflammatory response dominates. Interestingly, this also appears to be neurologically regulated. Recent studies suggest that efferent vagal nerve output reduces the inflammatory response through activation of nicotinic acetylcholine receptors on macrophage immune cells. This cholinergic antiinflammatory pathway has been demonstrated in rodent models [29] and may also contribute to other abdominal inflammatory disorders.

Over recent decades several drug therapies have been promoted as potentially beneficial in the amelioration of postoperative ileus. A recent Cochrane review of prokinetic agents in this setting studied 39 randomized controlled trials and showed that the use of many of these agents (including erythromycin, cholecystokinin, cisapride, and dopamine antagonists) is not supported by the available evidence [30].

As a result of new research into gastrointestinal motility, a number of novel pharmacologic therapies for postoperative ileus are in development. Among them, only two have reached clinical trials; and both seek to antagonize the Mu-opioid receptor in the gastrointestinal tract. Both endogenous and exogenous opioids are known to mediate reduced motility through their actions on gastrointestinal smooth muscle via this receptor. Previous difficulties in developing selective targets have been overcome, and two therapies that avoid antagonizing the beneficial effects of opioid-based analgesia have now reached Phase III trials [31]. Methylnaltrexone (Progenics Pharmaceuticals, Tarrytown, NY, USA) is a selective derivative of naltrexone undergoing evaluation in a randomized, double-blind trial of postcolectomy patients. Compared with placebo, methylnaltrexone significantly reduces morphine-induced delay in the gastrointestinal transit time and the peripheral side effects of morphine therapy [32, 33].

Alvimopan (Adolor, Exton, PA, USA) is a quaternary Mu-opioid receptor antagonist with a higher binding affinity than methylnaltrexone. A recent pooled analysis of Phase III trials studying its role in postoperative ileus has shown a clinically significant reduction in length of stay and postoperative morbidity rates [34]. However, a nonsignificant increase in the frequency of cardiovascular side effects has resulted in the U.S. Food and Drug Administration requesting further risk analysis prior to review [31].

Our analysis suggests beneficial effects from a considerably simpler and cheaper treatment strategy. However, the findings are limited by the small sample sizes. This potentially leads to a large variability in treatment effects due to random chance and so may overstate the findings. As with all studies of this nature, we are also open to risk of publication bias from the nonpublication of literature with negative findings in this area, as suggested by the funnel plots (Figs. 4, 5).

Several important methodological deficiencies were highlighted in the published research included in this analysis. Only one study included a placebo group to quantify the treatment effect [13], but because of their differing method of reporting results not all of their data could be included in our analysis. The study failed to report a statistical difference but showed a trend in favor of gum chewing. Another potential weakness is the lack of blinding in most studies, with potential bias by the surgical teams recording results. Blinding the participants would be difficult in this setting; however, blinding the observers is achievable and would lend weight to the findings. Another weakness is the widespread lack of standardization or description of perioperative care regimens. Given the known effects of opioids [35], epidural analgesia [36], and early enteral feeding [8–10] on subsequent patient recovery and postoperative ileus, it is unfortunate that several studies did not state postoperative practice in this respect. Equally, no definitions of discharge criteria were given in any of the studies to help interpret length of stay outcomes. This is particularly noticeable in the study by Asao et al., where despite patients undergoing laparoscopic colorectal surgery the mean length of stay was unusually long (mean 13.5 days for gum-chewing cohort, 14.5 days for the control group). Clarification was later published in which the author attributes this to the nature of private health insurance specific to the Japanese medical system [37].

One study (Kouba et al.) was excluded from our analysis because of its nonrandomized methodology [22] and another (Schluender et al.) because of insufficient data [16]. The results of Kouba et al. appear to add limited support to our findings in patients undergoing postradical cystectomy and urinary diversion. As the authors highlighted, this operation is suitable for comparison in that urinary diversion involves harvesting a segment of bowel with associated reanastamosis. In comparison to control patients, time to flatus (2.4 vs. 2.9 days; $P < 0.001$) and first bowel motion (3.2 vs. 3.9 days; $P < 0.001$) showed a clinically significant reduction in the treatment group. Length of stay was not significantly different with respect to controls (4.7 vs. 5.1 days; $P = 0.067$). Given that this was the largest study thus far, enrolling a total of 102 patients, it is disappointing that randomized, controlled trial methodology was not implemented.

In contrast, the second study excluded in our analysis did not support our findings. Schluender et al. enrolled 28 patients undergoing elective colonic surgery [16]. Twenty of them underwent open surgery, and eight underwent laparoscopic surgery; the results for the cohorts were analyzed separately. Although a trend toward shorter length of stay was seen in patients who participated in chewing gum therapy and underwent laparoscopic surgery, none of the results of this study were significant.

As this latter study demonstrated, a further potential confounder is the differing operations, indications, and pathologies included in the trials. Laparoscopic surgery is known to reduce the inflammatory response and in so doing promote a faster recovery [38]. Both case-matched studies and randomized controlled trials suggest a significant reduction in length of hospital stay for laparoscopy-assisted colonic surgery versus the traditional open technique [39, 40]. These different surgical interventions may cause variation in outcomes given the differing magnitude of ileus likely to result from open or laparoscopic procedures.

Table 1 Summary of postoperative complications

Study	Control group complications		Treatment group complications	
	Total events	Total patients	Total events	Total patients
Quah et al. [12]	14	19	15	19
Matros et al. [13]	10	21	4	22
Schuster et al. [14]	2	17	1	17
Hirayama et al. [15]	7	14	4	10
Asao et al. [18]	1	9	0	10

Table 2 Clinical outcomes in comparison to control groups (unspecified trials excluded)

Outcome	All included trials			Open surgery only			Laparoscopic surgery only		
	Reduction (weighted mean difference)	% Reduction compared to control	*P*	Reduction (weighted mean difference)	% Reduction compared to control	*P*	Reduction (weighted mean difference)	% Reduction compared to control	*P*
Time to first flatus (hours)	12.6	17	0.005	13.24	18	0.03	15.78	12	0.14
Time to first bowel opening (hours)	23.11	22	< 0.001	21.73	21	0.002	37.65	17	0.11
Length of stay (hours)	23.88	12	0.11	25.17	15	0.24	30.55	6	0.06

Interestingly, the study by McCormick et al. [17] demonstrated a benefit from chewing-gum therapy in the group treated laparoscopically but not in the group treated with open surgery. Likewise, a clear benefit was shown in the study by Asao et al. [18], where all patients underwent the laparoscopic technique. As previously described, the excluded study from Schluender et al. also described a trend toward reduced length of stay for patients given chewing-gum therapy who underwent laparoscopic colonic surgery, which was not seen in the open surgery cohort. Unfortunately, these results could not be included due to insufficient data for analysis. However, these findings suggest that the pathophysiologic changes in gastrointestinal motility resulting from open surgery may be more profound or complex than that generated by laparoscopic surgery—and thus more difficult to overcome with chewing-gum therapy. However, our subgroup analysis comparing laparoscopic with open surgery did not find a statistically significant difference between the results of these studies, although the laparoscopic surgery outcomes were nonsignificant when considered on their own.

Based on our existing knowledge of gastrointestinal motility and the factors affecting it, it is no surprise that gum-chewing, as a form of sham feeding, influences gut function [41]. After major gastrointestinal surgery, disorganized migrating motor complexes result in a lack of coordinated propulsion in intestinal and colonic smooth muscles. Spontaneous recovery usually occurs within 2–4 days, although it takes significantly longer in some patients. Recovery is also dependent on the segment of affected bowel. Motility in the small intestine usually returns to normal within 6–8 h, whereas that in the stomach may take 1–2 days and in the colon up to 6 days [42].

With this in mind, it is interesting to note the results of Chou et al., who looked specifically at effects of gum-chewing after subtotal gastrectomy. Their study failed to show a difference in bowel recovery and therefore supports the cephalic-vagal reflex as a significant component of the sham-feeding effect. However, to our knowledge no recent studies have sought to investigate these factors further. Despite these findings, recent research suggests that the well described cephalic-vagal reflex may not fully explain the changes in gastrointestinal motility associated with gum chewing. Sorbitol and other hexitols are common ingredients of sugar-free chewing gums and may act as osmotic laxitives, accelerating return of gastrointestinal motility [43]. It is regrettable that so few of the studies specified brand or ingredients in the gum used. Other research suggests that the role and rate of gum chewing act in an anxiolytic manner, with reduced systemic levels of

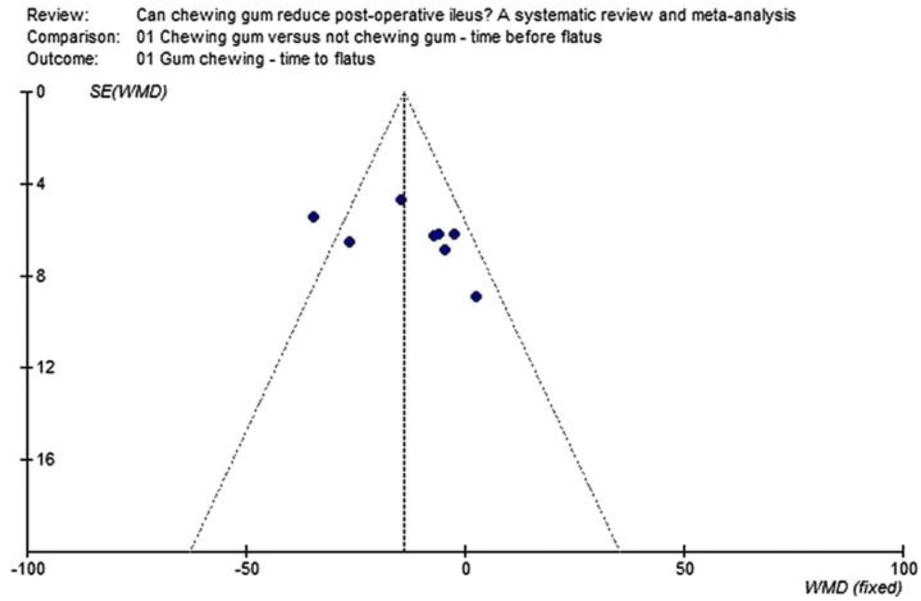

Fig. 4 Funnel plot of time to first flatus illustrating the degree of standard error by effect size

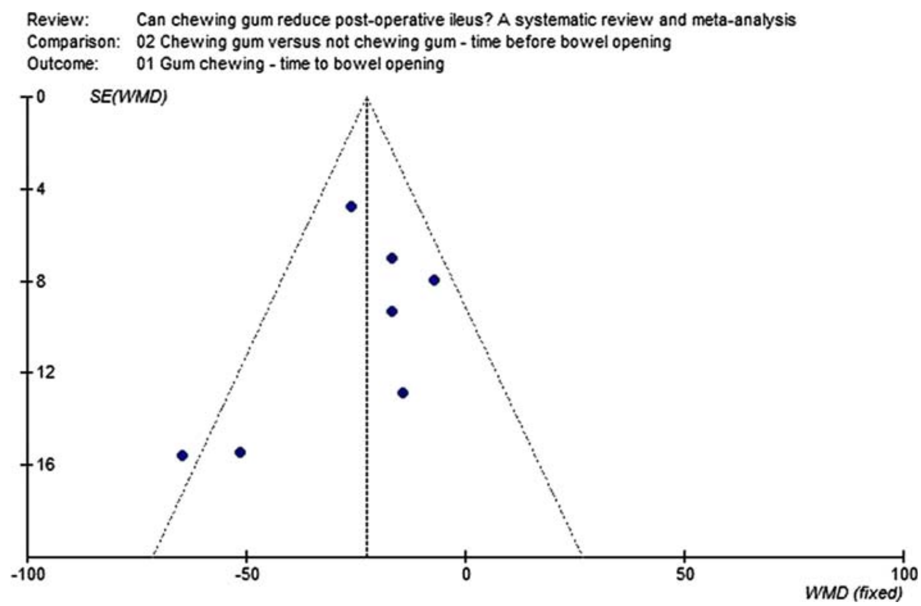

Fig. 5 Funnel plot of time to first bowel opening illustrating the degree of standard error by effect size

cortisol stress hormones [44, 45]. It is likely that the overall effects of gum chewing on gastrointestinal motility are multimodal and not yet fully understood. However, other groups are now exploiting the positive effect of gum chewing on gastrointestinal motility in other clinical settings by successfully accelerating the transit time for capsule endoscopy [46].

Although the articles reviewed in our analysis report similar complication rates among the study and control groups, it is important to note that chewing gum itself is not a risk-free therapy. The act of gum chewing has been shown to reduce short-term appetite through orosensory stimulation [47], which may have an effect on a patient's desire to recommence a normal diet. Several case reports highlight risks of bowel obstruction from swallowed gum [48], and cardiac arrest secondary to airway obstruction from inhaled gum has also been reported [49, 50]. Chewing-gum ingredients have been implicated in the causation of headaches (from aspartame, an artificial sweetner) [51], toxidermic vasculitis (from butylhydroxytoluene, a preservative) [52], and chronic diarrhea and weight loss (from sorbitol, a sweetener and emulsifier) [53].

Consideration of these risks must be balanced against potential benefits. Postoperative sedation may render patients at higher risk of aspiration, and a history of allergy or hypersensitivity to ingredients must act as a contraindication.

Conclusions

Our meta-analysis has shown that chewing gum during the postoperative period leads to a clinically significant reduction in time to passage of first flatus, time to first bowel motion, and a nonstatistically significant reduction in the length of inpatient stay following open gastrointestinal surgery. The validity of these conclusions is limited by the small number of trials available and their underlying heterogeneity. In addition, gum chewing may bring its own complications, and caution is therefore advised when introducing this therapy without considering the potential risks. We suggest that a large-scale randomized, placebo-controlled, multicenter trial is warranted to further investigate the relevance of chewing gum in the treatment of postoperative ileus. In addition, we reiterate the importance of investigators clearly defining, implementing, and reporting their studies in line with the CONSORT statement [54].

Neither author has any competing academic, personal, or commercial interests to declare. No funding was applied for or received in relation to the preparation of this manuscript.

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