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Randomized clinical trial

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Background: **Postoperative ileus is a common complication of abdominal surgery, leading to patient discomfort, morbidity and prolonged postoperative length of hospital stay (LOS). Previous studies suggested that chewing gum stimulates bowel function after abdominal surgery, but were underpowered to evaluate its effect on LOS and did not include enhanced recovery after surgery (ERAS)-based perioperative care. This study evaluated whether chewing gum after elective abdominal surgery reduces LOS and time to bowel recovery in the setting of ERAS-based perioperative care.**

Methods: **A multicentre RCT was performed of patients over 18 years of age undergoing abdominal surgery in 12 hospitals. Standard postoperative care (control group) was compared with chewing gum three times a day for 30 min in addition to standard postoperative care. Randomization was computer-generated; allocation was concealed. The primary outcome was postoperative LOS. Secondary outcomes were time to bowel recovery and 30-day complications.**

Results: **Between 2011 to 2015, 1000 patients were assigned to chewing gum and 1000 to the control arm. Median LOS did not differ: 7 days in both arms ($P = 0{\cdot}364$). Neither was any difference found in time to flatus (24 h in control group *versus* 23 h with chewing gum; $P = 0{\cdot}873$) or time to defaecation (60 *versus* 52 h respectively; $P = 0{\cdot}562$). The rate of 30-day complications was not significantly different either.**

Conclusion: **The addition of chewing gum to an ERAS postoperative care pathway after elective abdominal surgery does not reduce the LOS, time to bowel recovery or the rate of postoperative complications. Registration number: NTR2594 (Netherlands Trial Register).**

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Introduction

Postoperative ileus is common after abdominal surgery and is an important determinant of length of hospital stay (LOS)[1–3]. The Enhanced Recovery After Surgery (ERAS®) Society designed a multimodal perioperative care pathway to enhance recovery after abdominal surgery and reduce LOS[4–9]. One of the ERAS measures, early postoperative feeding, is considered effective in stimulating bowel movement, thereby possibly reducing postoperative ileus[10–13]. However, intolerance of oral intake owing to postoperative nausea and vomiting has been reported in up to 27 per cent of patients after abdominal surgery[14,15].

The concept of sham feeding is over a century old; it acts via the parasympathetic nervous system, stimulating bowel motility. The principle of preparing the bowel for food by activating the cephalic–vagal response was first described by Pavlov in the late 1800s[10]. Pavlov was the first to document that sham feeding had a similar effect on the gastrointestinal tract as 'normal' feeding[16]. The thought, sight, smell, taste and chewing of food induce the vagal nerve to release gastrointestinal hormones[17,18]. Chewing gum may elicit the same response as sham feeding by mimicking food intake. It has been shown[19–25] to stimulate the motility of the entire gastrointestinal tract and the secretion of saliva, gastrin and pancreatic juices. Therefore, sham feeding, including chewing gum, has been suggested as an attractive alternative to early postoperative feeding for the prevention of postoperative ileus. Other findings suggest that the hexitols in chewing gum have a beneficial effect on the restoration of bowel movement after abdominal surgery[26].

In several trials[27–34], postoperative chewing gum has been associated with a reduced time to gastrointestinal

and overall recovery, but often did not lead to a shorter LOS. A recent Cochrane review[35], which was based on 81 studies and included 9072 patients, showed that chewing gum reduced the time to first flatus by 10·6 h, the time to first bowel movement by 12·7 h and LOS by 0·7 days. The evidence, however, was considered to be of low quality and limited external validity, owing to the small sample sizes (the largest trial only included 500 patients, and the average number of patients per trial ranged from 20 to 50), the absence of a perioperative ERAS setting and the limited diversity of surgical procedures. The authors concluded there was a case for a large RCT that investigated the effect of adding chewing gum to ERAS postoperative care after abdominal surgery.

The present study was conducted accordingly, in an ERAS setting, and was designed to detect a clinically relevant difference in LOS in addition to bowel recovery. The study was designed to represent daily practice and to achieve high external validity. Patients were eligible for inclusion in the trial following various types of abdominal surgery. It was hypothesized that chewing gum would lead to a reduction in LOS of 1 day or more.

Methods

Study design and settings

This multicentre RCT was conducted in 12 hospitals in the Netherlands. The hospitals were selected based on their application of the ERAS protocol and included one academic centre and 11 teaching hospitals. Before starting, the trial was registered in the Netherlands Trial Register (NTR2594). All participating hospitals used the ERAS programme as their standard perioperative protocol. This protocol included an epidural catheter for 48 h followed by standard oral pain medication (paracetamol and opioids in a standard scheme), removal of the nasogastric tube directly after surgery (excluding oesophageal resection), mobilization on the day of surgery, and introduction and advancement of a free diet from the day of surgery or as soon as tolerated. Patients provided informed consent before randomization. Subsequently, web-based computer-generated randomization was performed before surgery using the minimization method.

All abdominal surgical procedures were included in this study, as the ERAS® Society principle was designed for abdominal surgery. Subgroups were created for intestinal and non-intestinal abdominal operations. Assignment to the treatment group was stratified based on hospital and on type of surgery: laparoscopic intestinal resection, intestinal surgery by laparotomy and non-intestinal surgery by laparotomy (for example vascular surgery). Patients were assigned randomly to either standard postoperative care (control group) or standard postoperative care plus 30 min of chewing gum three times per day (intervention group). The intervention was not supervised to mimic patient choice in early nutrition according to the ERAS protocol. Group allocation was concealed from the operating surgeon, medical staff providing postoperative care, and the physician or researcher who completed the trial case report form (CRF).

Participants

Patients eligible for participation in the trial were aged 18 years or more, and were undergoing either an elective laparotomy or laparoscopic intestinal resection or non-intestinal surgery by laparotomy. Exclusion criteria were emergency surgery, inability to provide informed consent, or risk of choking or dysphagia due to a pre-existing neurological disorder (such as after a stroke). The medical ethics committee of Leiden University Medical Centre and the institutional review boards of each of the 12 participating centres approved the trial, which was performed in accordance with the Declaration of Helsinki. No commercial sponsoring was received, specifically from chewing gum manufacturers.

Intervention

Patients in the intervention arm of the trial received chewing gum after surgery with the instruction to chew gum three times per day for 30 min starting on the day of surgery, and to continue as instructed until discharge from hospital. Patients in the control arm of the trial were instructed not to use chewing gum, and received standard postoperative care. The intervention was not recorded by the researchers; patients in the intervention arm self-reported their use of gum. The chewing gum intervention was added to the local ERAS protocol, which already included advised actions such as mobilization on the ward and early oral intake. The chewing gum used was sugarless Stimorol® Ice Peppermint (Mondelēz International, East Hanover, New Jersey, USA). Ingredients included natural and artificial flavours (sorbitol, maltitol syrup, xylitol, aspartame, acesulfame K), gum base, lustring agent (E903) and antioxidants (E321).

Outcomes

LOS, in days, was the primary outcome of the trial, starting from the day of surgery (day 0) and ending on the day of discharge from hospital. Secondary outcomes were

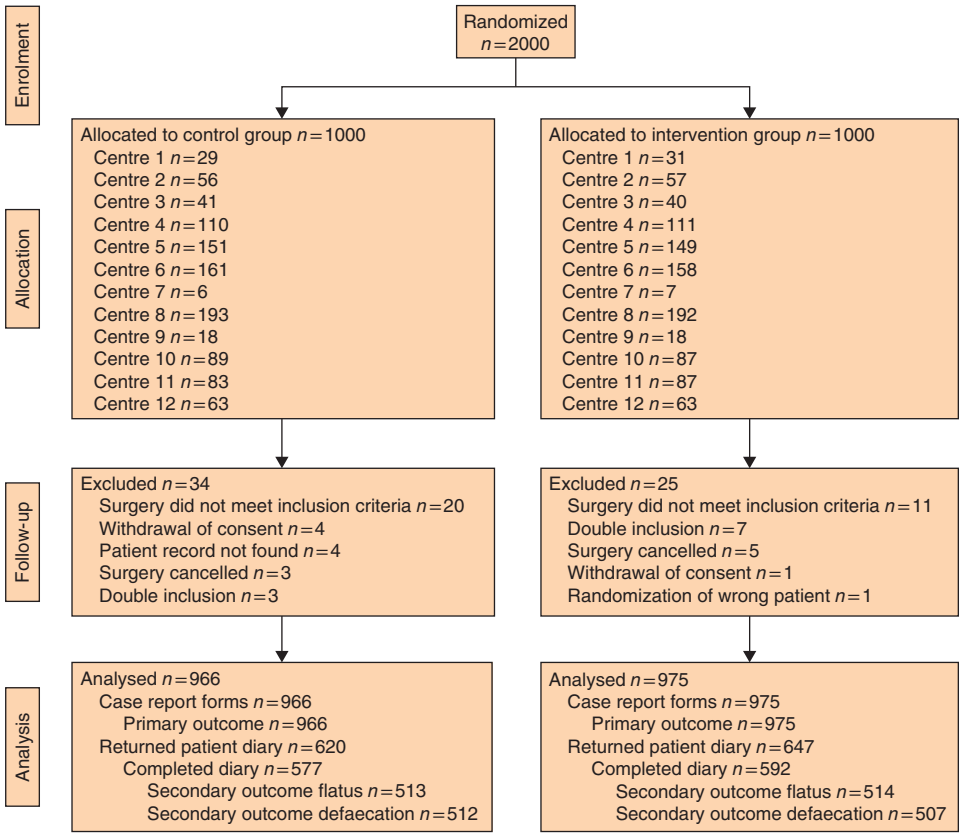

Fig. 1 CONSORT diagram of included patients. Patients in the control group received standard postoperative care; those in the intervention group received standard postoperative care and chewing gum

Table 1 Baseline characteristics of patients

	Control (*n* = 966)	Chewing gum (*n* = 975)
Age (years)*	66 (19–98)	66 (18–94)
Sex ratio (M : F)	565 : 401	552 : 423
ASA fitness grade	(*n* = 942)	(*n* = 958)
I	157 (16·7)	160 (16·7)
II	612 (65·0)	630 (65·8)
III	166 (17·6)	161 (16·8)
IV	7 (0·7)	7 (0·7)
BMI (kg/m^2)	25·4 (14·4–51·3)	25·5 (11·7–55·6)
Previous abdominal surgery	(*n* = 922)	(*n* = 944)
No	596 (64·6)	589 (62·4)
Yes (open and laparoscopic)	326 (35·4)	355 (37·6)
Malignancy	(*n* = 962)	(*n* = 973)
Yes	737 (76·6)	742 (76·3)
No	225 (23·4)	231 (23·7)

Values in parentheses are percentages unless indicated otherwise; *values are median (range).

partly patient reported, and included the time to flatus and time to defaecation. These secondary outcomes were calculated in hours and minutes from the end of surgery to the event reported by the patient in their diary. Both surgical and non-surgical 30-day complications were reported according to the Clavien–Dindo classification[36] in the CRF. Additional recorded data included the prolonged placement or reintroduction of a nasogastric tube after surgery and the use of epidural analgesia, antibiotics, opioids or laxatives.

Data were obtained from patients' diaries and the CRF. Patients filled out the diaries on a daily basis for the duration of their hospital stay. Before enrolment in the trial, a pilot study was performed using 20 patients to validate the diary questionnaire (data not reported). An outline of the questions in the diary is presented in Appendix S1 (supporting information). After an interim safety analysis, an eighth question to assess compliance was added to the diary, regarding the number of times the patient had chewed gum that day. The trial CRF was completed by the local clinicians 30 days after surgery or after discharge from the hospital using a web-based data form.

Sample size

A sample size calculation was based on the primary endpoint, postoperative LOS. The estimated median length of postoperative LOS was based on the results of the

Table 2 Details of surgical procedures

	Control ($n = 966$)	Chewing gum ($n = 975$)
Anatomical site of operation	($n = 949$)	($n = 954$)
Colon	471 (49·6)	529 (55·5)
Rectum	195 (20·5)	148 (15·2)
Combination	112 (11·8)	126 (13·2)
Other organs	69 (7·3)	72 (7·5)
Small intestine	42 (4·4)	40 (4·2)
Vascular surgery	36 (3·8)	23 (2·4)
Oesophagus/stomach	24 (2·5)	16 (1·7)
Ileostomy	97 (10·0)	59 (6·1)
Colostomy	130 (13·5)	123 (12·6)
Epidural analgesia	($n = 952$)	($n = 962$)
Yes	696 (73·1)	727 (75·6)
No	256 (26·9)	235 (24·4)
Surgical approach	($n = 964$)	($n = 972$)
Laparotomy	602 (62·4)	592 (60·9)
Laparoscopy	362 (37·6)	380 (39·1)
Duration of surgery (min)*	135 (10–479)	131 (10–558)
Operative blood loss (ml)*	150 (0–8360)	100 (0–6000)

Values in parentheses are percentages unless indicated otherwise; *values are median (range).

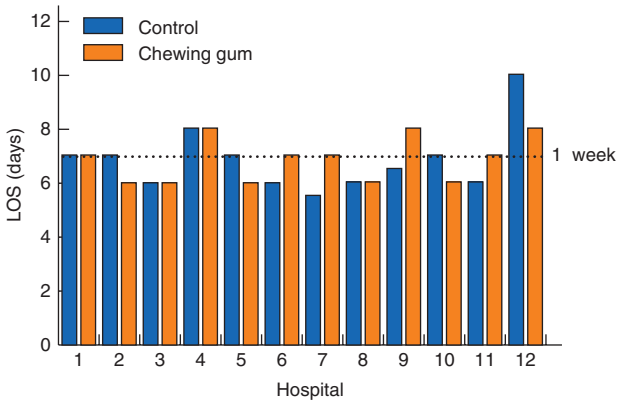

Fig. 2 Primary outcome, postoperative length of stay (LOS) in each of the 12 hospitals. $P = 0·702$ (two-way ANOVA)

meta-analysis performed by Noble *et al.*[28] in 2009. These calculations showed that a sample size of 2000 patients, equally spread in each arm of the study, would be required to detect a clinically relevant 1-day difference in LOS. The calculations were found to have 80 per cent power using a two-sided $P = 0·050$ with a median postoperative LOS of 8 days in the intervention group.

Statistical analysis

Reporting was in accordance with the CONSORT statement[37]. Statistical analysis was carried out using SPSS® version 23 (IBM, Armonk, New York, USA), and graphs were generated using GraphPad Prism® version 6.02 (GraphPad Software, San Diego, California, USA). All analyses were based on the principle of intention to treat, and all eligible patients were included in the analysis in the arm to which they were randomized, independently of whether they received the assigned treatment. The primary and secondary outcomes measured were compared using the Mann–Whitney *U* test, as the data were not normally distributed (both the Kolmogorov–Smirnov and Shapiro–Wilk tests of normality had $P < 0·001$). No imputation for missing data was performed. To analyse the data with a normally distributed variable, a new variable was created: $\log_{10}$ of the LOS data. Nominal data were analysed with the χ^2 test. The stratification subgroup interaction (hospital, surgical approach and surgical site) analysis was performed using a two-way ANOVA model, which included the two main factors and the interaction term. A two-tailed 5 per cent significance level was used.

Results

Participant flow

Between February 2011 and February 2015, 2000 patients were included in the trial and treated according to the local ERAS perioperative protocol. Patients were randomized to either the standard postoperative care group (control group, 1000 patients) or the standard care with the addition of chewing gum three times daily group (intervention group, 1000 patients). *Fig. 1* displays a flow chart of the inclusion of participants. Fifty-nine patients did not complete the study: 31 patients were wrongfully included as the type of surgery did not meet the inclusion criteria, ten were included twice and their second data forms were excluded, eight were excluded after cancellation of their surgical procedure, five withdrew their consent, four patients' records were missing at the time of completion of the CRF (most likely due to wrong identifiers – first three letters of last name and date of birth), and one patient was randomized accidently. Exclusion of these patients left 1941 patients eligible for analysis; 966 patients were in the control group and 975 in the intervention group.

The online CRF was completed for all included patients (100 per cent); 65·3 per cent of the diaries were returned, of which 92·3 per cent were filled out (93·1 per cent in the control group *versus* 91·5 per cent in the intervention group; $P = 0·297$).

Patient characteristics and surgical procedures

Baseline characteristics of the included patients and surgical procedures performed in the two groups are summarized in *Tables 1* and *2*. The median age of patients was 66 years, and 57·5 per cent of the patients were men. The

Table 3 Primary and secondary outcomes

	Control ($n = 966$)	Chewing gum ($n = 975$)	P†
Primary outcome			
LOS (days)			
Median (i.q.r.)	7 (5–10)	7 (5–10)	0·364
Log_{10} LOS*	0·876(0·260)	0·868(0·273)	0·471
Anatomical site of surgery (median LOS)			
Colon	6	6	
Rectum	8	6	
Combination	8	8	
Other organs	7	6	
Small intestine	5	7	
Vascular surgery	8	8	
Oesophagus/stomach	10	8	
Miscellaneous	5	7	
Surgical approach (median LOS)			0·914
Laparoscopy	6	6	
Laparotomy	7	7	
Secondary outcomes			
Time to first flatus (h)	($n = 406$)	($n = 412$)	
Median (i.q.r.)	24 (13–48)	23 (14–45)	0·873
Time to first defaecation (h)	($n = 426$)	($n = 424$)	
Median (i.q.r.)	60 (25–88)	52 (29–79)	0·562
Complications	($n = 965$)	($n = 975$)	
Yes	371 (38·4)	341 (35·0)	0·113‡
Death	9 (0·9)	12 (1·2)	0·833‡
Surgical complications			
Bleeding	11 (1·1)	18 (1·8)	
Wound infection/abscess	90 (9·3)	87 (8·9)	
Ileus	105 (10·9)	92 (9·4)	
Anastomotic leakage	39 (4·0)	43 (4·4)	
Wound dehiscence	8 (0·8)	9 (0·9)	
Iatrogenic	15 (1·6)	15 (1·5)	
Other	31 (3·2)	29 (3·0)	
Non-surgical complications			
Cardiac	23 (2·4)	33 (3·4)	
Neurological	13 (1·3)	8 (0·8)	
Infection, pulmonary	56 (5·8)	57 (5·8)	
Infection, other	57 (5·9)	48 (4·9)	
Thromboembolism	11 (1·1)	11 (1·1)	
Other	7 (0·7)	70 (7·2)	
Readmission within < 30 days	70 (7·3)	57 (5·8)	
ICU admission	45 (4·7)	51 (5·2)	

Values in parentheses are percentages unless indicated otherwise; *s.d. values are shown in parentheses. LOS, length of hospital stay. †Mann–Whitney U test, except ‡χ^2 test.

majority had an ASA fitness grade[38] of II, and a mean BMI of 26. Most patients had surgery for an oncological indication. Baseline patient characteristics did not differ between the two groups. The majority of procedures were colonic resections, and most patients received epidural analgesia. Almost 40 per cent of procedures were laparoscopic.

Outcomes

Primary outcome: length of hospital stay

The primary outcome was assessed for 100 per cent of included patients (*Table 3*). Median LOS was not significantly different between groups, at 7 days for both groups ($P = 0·364$). The log_{10} LOS also did not differ: 0·876 *versus* 0·868 for the control and intervention group respectively ($P = 0·471$), which corresponds to 7·5 *versus* 7·4 days.

Analyses corrected for hospital, surgical approach and anatomical site (intestinal or non-intestinal) were performed. Subgroup by treatment interaction analyses were not significant, indicating that the effect of chewing gum on LOS was not affected by hospital ($P = 0·702$, $R^2 = 0·042$) (*Fig. 2*), surgical approach ($P = 0·924$, $R^2 = 0·007$) or anatomical site ($P = 0·694$, $R^2 = 0·001$).

Secondary outcomes: time to flatus and defaecation

The median time to flatus was not significantly different between control and intervention groups (24 *versus* 23 h

respectively; $P = 0{\cdot}873$). Neither was time to defaecation: 60 *versus* 52 h respectively ($P = 0{\cdot}562$).

Complications

The number of complications did not differ between the two groups. Surgical complications included ileus, defined as the mention of ileus or gastroparesis in the patient's record by the treating physician; anastomotic leakage, defined by imaging and requiring surgical or radiological intervention; and iatrogenic complications, such as iatrogenic injury during surgery or resulting from a surgical intervention in the postoperative phase. No adverse events related to chewing gum were reported. One or more complications were reported in 712 (36·7 per cent) of the 1941 CRFs. In 220 (11·3 per cent) a radiological or surgical intervention was required, and 96 patients (4·9 per cent) required admission to the ICU. The 30-day postoperative mortality rate was 1·1 per cent (21 patients); of these, 12 were patients in the intervention group. None of these deaths were related to chewing gum. Patients who did not return or complete their diary did not experience more complications than those who did ($P = 0{\cdot}122$).

Compliance

At the time of interim analysis, after the inclusion of 500 patients, it appeared that compliance to chewing gum was not 100 per cent. Thereafter, as described in the methods section, an additional question was added to the diary in an attempt to monitor compliance with the chewing gum protocol. However, this question was not completed in the majority of diaries, and thus chewing gum compliance could not be determined adequately. Of the 975 patients in the intervention group, 78 (8·0 per cent) reported that they did not chew gum on days 1–3. Their feedback indicated that this lack of compliance was due primarily to nausea, malaise or the belief that the chewing gum would stick to dentures.

Discussion

In this large multicentre RCT of postoperative chewing gum, no benefit in LOS was found following the use of chewing gum in the postoperative phase after elective abdominal surgery.

Several previous trials have investigated the effect of chewing gum on gastrointestinal recovery after surgery. Since the ERAS principle was advocated in 2000 by Kehlet and co-workers, care providers have been paying more attention to perioperative care regimens[4,39]. Subsequently there has been increasing interest in using chewing gum after gastrointestinal surgery as sham feeding. This has resulted in numerous clinical trials, the first of which was published by Asao *et al.*[40] in 2002. The majority of these publications report enhanced recovery of bowel movements after gastrointestinal surgery or a reduced LOS after chewing gum[27,29,30,34,41]. This reduction was not always clinically significant; a few hours' difference in bowel movement often did not result in a reduction of LOS. Most of these studies involved small patient numbers and had very specific inclusion criteria, such as 'left-sided colon or rectal cancer surgery' only[42–45].

The 2009 meta-analysis by Noble and colleagues[28] served as the basis for the present RCT. Noble *et al.* concluded that chewing gum was associated with a reduction in complications. The data available for this meta-analysis were insufficient, and the authors stated that an adequately powered and well designed trial would be required to confirm the potential benefits of chewing gum[28]. In the more recent Cochrane review[35], a modest reduction in LOS of 0·7 days was found, and time to bowel recovery was also improved only moderately (10·6 *versus* 12·7 h). The authors[35] described statistical heterogeneity between the studies included in the analyses, especially with respect to postoperative care pathways and the frequency and duration of chewing gum. Additionally, compliance and its monitoring were heterogeneous[46]. In addition to the heterogeneity, Short and co-workers[35] reported that methodology and allocation were poorly described in the included trials, with only a few studies describing the use of sample-size or power calculations. Finally, the mean number of included patients per study was low (122, range 18–500), and the type of operation was mostly colorectal surgery or caesarean section.

In the present study, the endpoints of LOS, time to flatus and time to defaecation were determined based on the study of Noble *et al.*[28]. These variables were measurable endpoints and could be self-reported by the patient. Van Bree and colleagues[47] later concluded that the time to toleration of solid food and time to first defaecation best reflect recovery of gastrointestinal transit. With this knowledge, the present authors recommend other primary and secondary endpoints for any future trials of this kind, such as the GI-2 criteria (GI-2: time to first tolerated solid food and time to first bowel movement), which have been used before.

The present trial included 2000 patients with various co-morbidities, including previous abdominal surgery, who underwent a range of elective abdominal surgery with no upper restriction on age. The sample size of the study was calculated to detect a clinically relevant decrease in LOS (24 h) with a power of 80 per cent. Funnel plots in the Cochrane review[35] suggested a publication bias for time to bowel movement and LOS; this was also suggested in

the forest plot of trials included in the meta-analysis by Ho and colleagues[48], in which eight of the ten included trials favoured the use of chewing gum. Based on the potential publication bias, Ho *et al.*[48] concluded that the addition of chewing gum in the postoperative phase has no advantage when patients start oral intake soon after surgery, which is already an important part of the ERAS® Society protocol recommendations. The outcome of the present trial is among the few reporting no beneficial effect of adding chewing gum to an ERAS protocol[45,49–51].

Several types of abdominal surgical procedure were included in this trial, providing a broad overview of the effect of adding chewing gum to an existing postoperative protocol. Upper gastrointestinal and vascular surgery may involve different postoperative feeding regimens, but as similar proportions of patients in the two groups had these types of operation, analyses were performed for these subgroups. None of the previous studies on gum chewing reported the number of patients for whom gum chewing was not feasible after surgery[28,35]. This study was started without systematic recording of the intervention. However, during the trial, the research team encountered some patients who did not tolerate gum chewing for reasons such as nausea. After the interim analysis, recording of the intervention was started. Not all compliance self-reporting was completed in the patient diaries, indicating a difficulty in compliance monitoring. It was hypothesized that patients with incomplete diaries might not have been able to complete the reports due to physical discomfort. As nausea is a universal common symptom after abdominal surgery, the degree of non-compliance with gum chewing may warrant future investigation. Although non-compliance is a limitation of the present trial, the authors propose that the results do represent the real effect of introducing a measure such as gum chewing into daily practice, where patients will not be forced, but only encouraged, to use an intervention, similar to early feeding as part of the ERAS protocol.

In the present study, patient-reported outcomes were collected, providing a large amount of postoperative data. An attempt was made to collect data from all patients, and 65·3 per cent of the diaries were collected successfully. If patients did not return their diary at discharge, they were called on at home, requesting return of the diary to the hospital. No outcome differences were found in the CRFs of patients who did and those who did not return the diary, suggesting that these patient-reported outcomes are representative of all included patients. The study protocol involved the introduction of an unsupervised intervention, and compliance monitoring was not complete for all patients. This factor may have influenced the results of the intention-to-treat analysis. This is, however, a representation of daily practice. In addition, the authors tried to investigate compliance by including an additional question in the patient diary. It is not known why all patients did not answer this question, although one reason might be that some patients were not willing to admit that they did not follow the instructed protocol of chewing gum three times per day. Other patients reported that they did not chew gum because of nausea or fear that the gum would stick to their dentures. These limitations of chewing gum have not been reported in previous studies, nor are they mentioned in the Cochrane review[35].

Based on the findings of this multicentre RCT, the addition of chewing gum to an institutionalized ERAS protocol following elective abdominal surgery did not decrease the LOS, time to first flatus or time to first defaecation. A possible explanation is that LOS had already been maximally optimized with the current ERAS protocol.

Collaborators

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References

1 Asgeirsson T, El-Badawi KI, Mahmood A, Barletta J, Luchtefeld M, Senagore AJ. Postoperative ileus: it costs more than you expect. *J Am Coll Surg* 2010; **210**: 228–231.
2 Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. *J Manag Care Pharm* 2009; **15**: 485–494.
3 Gan TJ, Robinson SB, Oderda GM, Scranton R, Pepin J, Ramamoorthy S. Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries. *Curr Med Res Opin* 2015; **31**: 677–686.
4 Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000; **232**: 51–57.
5 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–617.
6 Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C *et al.* Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations – Part II. *Gynecol Oncol* 2016; **140**: 323–332.
7 Maessen JM, Dejong CH, Kessels AG, von Meyenfeldt MF; Enhanced Recovery After Surgery (ERAS) Group. Length of stay: an inappropriate readout of the success of enhanced recovery programs. *World J Surg* 2008; **32**: 971–975.
8 Eskicioglu C, Forbes SS, Aarts MA, Okrainec A, McLeod RS. Enhanced Recovery After Surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. *J Gastrointest Surg* 2009; **13**: 2321–2329.
9 de Groot JJ, Ament SM, Maessen JM, Dejong CH, Kleijnen JM, Slangen BF. Enhanced recovery pathways in abdominal gynecologic surgery: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2016; **95**: 382–395.
10 Stern RM, Crawford HE, Stewart WR, Vasey MW, Koch KL. Sham feeding. Cephalic–vagal influences on gastric myoelectric activity. *Dig Dis Sci* 1989; **34**: 521–527.
11 Reissman P, Teoh TA, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. *Ann Surg* 1995; **222**: 73–77.
12 Watters JM, Kirkpatrick SM, Norris SB, Shamji FM, Wells GA. Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. *Ann Surg* 1997; **226**: 369–377.
13 Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding *versus* 'nil by mouth' after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *BMJ* 2001; **323**: 773–776.
14 Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: a prospective randomized trial. *Aust N Z J Surg* 1998; **68**: 125–128.
15 Petrelli NJ, Cheng C, Driscoll D, Rodriguez-Bigas MA. Early postoperative oral feeding after colectomy: an analysis of factors that may predict failure. *Ann Surg Oncol* 2001; **8**: 796–800.
16 Collinger JL, Boninger ML, Bruns TM, Curley KC, Wang W, Weber DJ. Attitude towards brain–computer interface technology among veterans with spinal cord injury. *Top Spinal Cord Inj Rehabil* 2011; **16**: 61–62.
17 Feldman M, Richardson CT. Role of thought, sight, smell, and taste of food in the cephalic phase of gastric acid secretion in humans. *Gastroenterology* 1986; **90**: 428–433.
18 Moore JG, Schenkenberg T. Psychic control of gastric acid: response to anticipated feeding and biofeedback training in a man. *Gastroenterology* 1974; **66**: 954–959.
19 Wøjdemann M, Wettergren A, Hartmann B, Hilsted L, Holst JJ. Inhibition of sham feeding-stimulated human gastric acid secretion by glucagon-like peptide-2. *J Clin Endocrinol Metab* 1999; **84**: 2513–2517.
20 Soffer EE, Adrian TE. Effect of meal composition and sham feeding on duodenojejunal motility in humans. *Dig Dis Sci* 1992; **37**: 1009–1014.
21 Konturek SJ, Thor P. Relation between duodenal alkaline secretion and motility in fasted and sham-fed dogs. *Am J Physiol* 1986; **251**(Pt 1): G591–G596.
22 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**: 53–56.
23 Miedema BW, Schillie S, Simmons JW, Burgess SV, Liem T, Silver D. Small bowel motility and transit after aortic surgery. *J Vasc Surg* 2002; **36**: 19–24.
24 Feldman M, Richardson CT, Fordtran JS. Experience with sham feeding as a test for vagotomy. *Gastroenterology* 1980; **79**(Pt 1): 792–795.
25 Huge A, Kreis ME, Zittel TT, Becker HD, Starlinger MJ, Jehle EC. Postoperative colonic motility and tone in patients after colorectal surgery. *Dis Colon Rectum* 2000; **43**: 932–939.
26 Tandeter H. Hypothesis: hexitols in chewing gum may play a role in reducing postoperative ileus. *Med Hypotheses* 2009; **72**: 39–40.
27 van den Heijkant TC, Costes LM, van der Lee DG, Aerts B, Osinga-de Jong M, Rutten HR *et al.* Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. *Br J Surg* 2015; **102**: 202–211.
28 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**: 100–105.
29 Su'a BU, Pollock TT, Lemanu DP, MacCormick AD, Connolly AB, Hill AG. Chewing gum and postoperative

ileus in adults: a systematic literature review and meta-analysis. *Int J Surg* 2015; **14**: 49–55.
30 Yin Z, Sun J, Liu T, Zhu Y, Peng S, Wang J. Gum chewing: another simple potential method for more rapid improvement of postoperative gastrointestinal function. *Digestion* 2013; **87**: 67–74.
31 Grupa Robocza Europejskiego Towarzystwa Kardiologicznego (ESC) do spraw rozpoznawania i postepowania w kardiomiopatii przerostowej, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F *et al.* [2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy.] *Kardiol Pol* 2014; **72**: 1054–1126.
32 Li S, Liu Y, Peng Q, Xie L, Wang J, Qin X. Chewing gum reduces postoperative ileus following abdominal surgery: a meta-analysis of 17 randomized controlled trials. *J Gastroenterol Hepatol* 2013; **28**: 1122–1132.
33 Shum NF, Choi HK, Mak JC, Foo DC, Li WC, Law WL. Randomized clinical trial of chewing gum after laparoscopic colorectal resection. *Br J Surg* 2016; **103**: 1447–1452.
34 Topcu SY, Oztekin SD. Effect of gum chewing on reducing postoperative ileus and recovery after colorectal surgery: a randomised controlled trial. *Complement Ther Clin Pract* 2016; **23**: 21–25.
35 Short V, Herbert G, Perry R, Atkinson C, Ness AR, Penfold C *et al.* Chewing gum for postoperative recovery of gastrointestinal function. *Cochrane Database Syst Rev* 2015; (2)CD006506.
36 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.
37 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357**: 1191–1194.
38 Fitz-Henry J. The ASA classification and peri-operative risk. *Ann R Coll Surg Engl* 2011; **93**: 185–187.
39 Basse L, Raskov HH, Hjort Jakobsen D, Sonne E, Billesbølle P, Hendel HW *et al.* Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg* 2002; **89**: 446–453.
40 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**: 30–32.
41 Schuster R, Grewal N, Greaney GC, Waxman K. Gum chewing reduces ileus after elective open sigmoid colectomy. *Arch Surg* 2006; **141**: 174–176.
42 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.
43 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**: 44–46.
44 Ngowe MN, Eyenga VC, Kengne BH, Bahebeck J, Sosso AM. Chewing gum reduces postoperative ileus after open appendectomy. *Acta Chir Belg* 2010; **110**: 195–199.
45 Kobayashi T, Masaki T, Kogawa K, Matsuoka H, Sugiyama M. Efficacy of gum chewing on bowel movement after open colectomy for left-sided colorectal cancer: a randomized clinical trial. *Dis Colon Rectum* 2015; **58**: 1058–1063.
46 Atkinson C, Penfold CM, Ness AR, Longman RJ, Thomas SJ, Hollingworth W *et al.* Randomized clinical trial of postoperative chewing gum *versus* standard care after colorectal resection. *Br J Surg* 2016; **103**: 962–970.
47 van Bree SH, Bemelman WA, Hollmann MW, Zwinderman AH, Matteoli G, El Temna S *et al.* Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus. *Ann Surg* 2014; **259**: 708–714.
48 Ho YM, Smith SR, Pockney P, Lim P, Attia J. A meta-analysis on the effect of sham feeding following colectomy: should gum chewing be included in enhanced recovery after surgery protocols? *Dis Colon Rectum* 2014; **57**: 115–126.
49 Matros E, Rocha F, Zinner M, Wang J, Ashley S, Breen E *et al.* Does gum chewing ameliorate postoperative ileus? Results of a prospective, randomized, placebo-controlled trial. *J Am Coll Surg* 2006; **202**: 773–778.
50 Lim P, Morris OJ, Nolan G, Moore S, Draganic B, Smith SR. Sham feeding with chewing gum after elective colorectal resectional surgery: a randomized clinical trial. *Ann Surg* 2013; **257**: 1016–1024.
51 Zaghiyan K, Felder S, Ovsepyan G, Murrell Z, Sokol T, Moore B *et al.* A prospective randomized controlled trial of sugared chewing gum on gastrointestinal recovery after major colorectal surgery in patients managed with early enteral feeding. *Dis Colon Rectum* 2013; **56**: 328–335.

Supporting information

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