Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II)

Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II): a multicentre, double-blind, randomised controlled trial

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Summary

Background **Postoperative ileus and anastomotic leakage severely impair recovery after colorectal resection. We investigated the effect of perioperative lipid-enriched enteral nutrition versus standard care on the risk of postoperative ileus, anastomotic leakage, and other clinical outcomes.**

Methods **We did an international, multicentre, double-blind, randomised, controlled trial of patients (≥18 years) undergoing elective colorectal surgery with primary anastomosis at six clinical centres in the Netherlands and Denmark. Patients were randomly assigned (1:1), stratified by location (colonic and rectal) and type of surgery (laparoscopic and open), via online randomisation software, with block sizes of six, to receive either continuous lipid-enriched enteral tube feeding from 3 h before until 6 h after surgery (intervention) or no perioperative nutrition (control). Surgeons, patients, and researchers were masked to treatment allocation for the entire study period. The primary outcome was postoperative ileus. Secondary outcomes included anastomotic leakage, pneumonia, preoperative gastric volumes, time to functional recovery, length of hospital stay, the need for additional interventions, intensive care unit admission, postoperative inflammatory response, and surgical complications. Analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT02175979, and trialregister.nl, number NTR4670.**

Findings **Between July 28, 2014, and February 20, 2017, 280 patients were randomly assigned, 15 of whom were excluded after random allocation because they fulfilled one or more exclusion criteria. 265 patients received perioperative nutrition (n=132) or standard care (n=133) and were included in the analyses. A postoperative ileus occurred in 37 (28%) patients in the intervention group versus 29 (22%) in the control group (risk ratio [RR] 1·09, 95% CI 0·95–1·25; p=0·24). Anastomotic leakage occurred in 12 (9%) patients in the intervention group versus 11 (8%) in the control group (RR 1·01, 95% CI 0·94–1·09; p=0·81). Pneumonia occurred in ten (8%) patients in the intervention group versus three (2%) in the control group (RR 1·06, 95% CI 1·00–1·12; p=0·051). All other secondary outcomes were similar between groups (all p>0·05).**

Interpretation **Perioperative lipid-enriched enteral nutrition in patients undergoing elective colorectal surgery has no advantage over standard care in terms of postoperative complications.**

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Introduction

Postoperative outcomes in colorectal surgery have improved with the introduction of enhanced recovery after surgery (ERAS) programmes.[1] However, postoperative complications continue to impair recovery and increase health-care costs. In particular, postoperative ileus is a common complication and is associated with a prolonged length of hospital stay.[2]

Early initiation of oral intake is an independent determinant of early recovery in ERAS protocols.[3] Furthermore, early enteral nutrition reduces not only postoperative ileus but also anastomotic leakage after major rectal surgery.[4] Anastomotic leakage is a major determinant for postoperative recovery. However, beneficial effects of early oral intake on postoperative ileus and anastomotic leakage were not seen in other studies.[5] Despite extensive research, no therapeutic options to reduce postoperative ileus and anastomotic leakage are available, and the incidence of these complications has remained stable.[6,7]

The inflammatory response is essential in the development of postoperative ileus, and is likely to also play an important part in anastomotic leakage.[8,9] In postoperative ileus, opening of the peritoneal cavity and intestinal manipulation induce the release of inflammatory mediators that impair gastrointestinal motility.[9] In experimental studies, enteral nutrition reduced postoperative ileus by dampening the inflammatory response via a mechanism that involves

Research in context

Evidence before this study

Experimental studies by our group identified a novel potential therapeutic target to reduce postoperative ileus by dampening the inflammatory response via enteral nutrition given just before, during, and directly after surgery. We searched for randomised clinical trials on PubMed, Cochrane, Embase, and MEDLINE using all synonyms regarding the intervention "enteral nutrition", and the domain "colorectal surgery", with no language restrictions (updated until Dec 1, 2017). Studies were included that compared oral or enteral nutrition versus standard care (ie, nil by mouth) given just before, during, or within 24 h after elective colorectal surgery in patients aged 18 years or older. Studies using immunonutrition were excluded. No clinical studies had reported the effect of enteral nutrition on inflammation, or on enteral nutrition administrated continuously before, during, and after colorectal resection. Five studies reported on the effect of early postoperative enteral nutrition compared with standard care (ie, late start of oral intake) on postoperative ileus. In these studies, postoperative ileus was not well defined and no effect of enteral nutrition was found. Findings from published meta-analyses of randomised studies suggested an increased incidence of vomiting and faster passage of flatus in patients fed early; however, other surrogate markers of postoperative ileus were similar between groups. Overall, the available clinical literature on this subject is scarce and of poor methodological quality. In a recent randomised controlled trial by our group, a beneficial effect on anastomotic leakage was noted when postoperative ileus was reduced by means of early enteral versus parenteral nutrition after major rectal surgery. However, other published work on the effect of early enteral nutrition following colorectal surgery found no effect on anastomotic leakage, as shown in a 2017 systematic review. Existing studies are heterogeneous with regards to definitions of anastomotic leakage, methodological quality, and clinical characteristics. Taken together, the effect of enteral nutrition given continuously before, during, and directly after colorectal surgery was unclear in a clinical setting.

Added value of this study

Postoperative ileus and anastomotic leakage are major determinants of clinical outcomes after colorectal surgery. The promising results of experimental and preclinical studies on the effect of perioperative enteral nutrition on postoperative ileus from our group had thus far not been substantiated into a clinical setting, and in general there is little high-quality clinical evidence on the effect of enteral nutrition on postoperative ileus and anastomotic leakage. Reducing these complications using an inexpensive and feasible intervention such as perioperative nutrition would substantially improve postoperative outcomes and markedly reduce health-care costs. In the SANICS II trial, lipid-enriched enteral nutrition given just before, during, and directly after colorectal surgery was compared with standard of care. We found no evidence of an improvement in postoperative ileus (primary endpoint) or anastomotic leakage (a secondary endpoint).

Implications of the available evidence

By contrast with findings from previous experimental and preclinical studies, the administration of perioperative lipid-enriched enteral nutrition did not reduce the incidence of postoperative ileus and anastomotic leakage after colorectal surgery when investigated in a clinical setting. This study shows that the results from extensive experimental and preclinical studies are not necessarily valid in a clinical setting, which underscores the importance of high-quality, randomised studies.

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activation of the autonomic nervous system.[10] This activation is the result of the enhanced availability of specific lipids and proteins that stimulate the release of cholecystokinin, which binds to cholecystokinin receptors expressed on afferent vagal fibres in the small intestine. Subsequent vagal reflex activity can inhibit the inflammatory response.[11] The timing and composition of nutrition are essential; optimum effects are established when lipid-enriched nutrition is given just before, during, and directly after the inciting event continuously or via a bolus in low volumes.[12] In a clinical setting, the continuous administration of enteral nutrition just before, during, and directly after surgery to stimulate the autonomic nervous system is controversial and does not conform with American Society of Anaesthesiology guidelines.[13] We validated that autonomic nervous system stimulation via chewing gum effectively reduced postoperative inflammation in patients undergoing colorectal surgery.[14] Additionally, we showed a concomitant beneficial effect on both postoperative ileus and anastomotic leakage in the group treated with chewing gum.[14]

In this double-blind, randomised controlled trial, we investigated the effect of lipid-enriched enteral nutrition administration just before, during, and directly after colorectal surgery on postoperative ileus and anastomotic leakage.

Methods

Study design and participants

This international, multicentre, double-blind, parallel, randomised controlled trial was done from July 28, 2014, to March 22, 2017, in six hospitals in the Netherlands and Denmark. We followed the principles of Good Clinical Practice and the Declaration of Helsinki, and a Data Safety Monitoring Board (DSMB) monitored serious adverse events every ten consecutively enrolled and randomly assigned patients.

Patients aged at least 18 years undergoing elective segmental colorectal resection with primary anastomosis were eligible for inclusion. Exclusion criteria were a previous gastric or oesophageal resection, peritoneal carcinomatosis, a pre-existing or the creation of an

ileostomy, and use of glucocorticosteroids or drugs that disrupt acetylcholine metabolism (eg, selective serotonin-reuptake inhibitors or anticonvulsants).

Patient recruitment began in the Catharina Hospital (Eindhoven, Netherlands) on July 28, 2014. After a safety analysis was done for the first 40 consecutively enrolled and randomly assigned patients, the DSMB approved expansion of the trial to the following participating centres: Máxima Medical Centre (Veldhoven, Netherlands), Elkerliek Hospital (Helmond, Netherlands), Aarhus University Hospital (Aarhus, Denmark), Randers Regional Hospital (Randers, Denmark), and Viborg Regional Hospital (Viborg, Denmark). Patients were enrolled by trained investigators at each site. After 140 patients were randomly assigned, an interim analysis of the primary and relevant secondary outcomes (postoperative ileus, anastomotic leakage, aspiration pneumonia, length of stay, and mortality) was done by the DSMB to assess the benefit or potential harm of the intervention. The results of the interim analysis did not prompt the DSMB to prematurely terminate the study, and recruitment continued.

See Online for appendix

The study protocol was approved by the Medical Ethics Committee of the Catharina Hospital under reference number NL45640.060.13 and has been published.[15] The institutional review board of each participating hospital approved the protocol. All patients provided written informed consent before enrolment.

Randomisation and masking

The day before surgery, all patients received a self-migrating nasojejunal tube (Bengmark, Nutricia Flocare, Zoetermeer, Netherlands) at the surgical ward. An abdominal x-ray was done to assess whether the tube had migrated post pylorically after 7–24 h. Patients were excluded if post-pyloric tube migration was unsuccessful. Patients in whom the tube had migrated successfully were randomly assigned (1:1) to continuous lipid-enriched enteral tube feeding (intervention group) or no perioperative nutrition (control group) by external online randomisation software (TENALEA Clinical Trial Data Management System, Amsterdam, Netherlands), with a block size of six and stratified by site. Additionally, we used masked stratification to ensure an equal distribution between colonic and rectal surgery and between laparoscopic and open procedures. During randomisation, a number was generated that corresponded to an envelope containing a branched tubing system (ECM Europe BV, Gemert, Netherlands). These tubing systems were packed in identical, sealed envelopes labelled by independent research nurses with a randomisation number from an allocation list provided by TENALEA. The tubing system, specially designed for the double-blind nature of the study, was opaque and bifurcated into two branches. One branch was connected to the Bengmark tube in the patient, and the other branch was connected to a black container that was attached to the bed. One of the branches was occluded at the bifurcation by the manufacturer. For patients allocated to the intervention group, the tubing system was open towards the patient and closed towards the black container. Conversely, for patients allocated to the control group, the tubing system was closed towards the patient and open towards the black container. Consequently, only patients in the intervention group received lipid-enriched enteral nutrition. The containers were sealed and weighted with 4–6 L of saline; thus, any possible changes in weight from the added nutrition would be imperceptible to the patients and supporting medical and research staff.

Procedures

In all patients in the intervention group, lipid-enriched enteral nutrition (Nutricia Research, Utrecht, Netherlands) was administered via an electronic feeding pump at a rate of 1·5 mL/min. The composition of the enteral formula is described in the appendix (p 1). The enteral nutrition was administered perioperatively: the feeding pump was started 3 h before the planned onset of surgery, continued during the operation, and stopped 6 h after ending the surgical procedure. The time of cessation was chosen because patients generally initiated oral intake at this time and were offered enteral nutrition at about 6 h after surgery according to ERAS guidelines.[1] After nutrition was stopped, the nasojejunal tube was flushed with 20 mL of saline to remove any potential residue. After disconnecting from the patient, the masked tubing sets and black containers were retained until ten procedures had been done before being disposed of by independent research nurses.

All patients were treated according to the principles of the ERAS protocols. In the Danish centres, ERAS protocols had been gradually implemented since the end of the 1990s, whereas all Dutch centres received formal training when ERAS was introduced in 2006. The ERAS protocols of the participating hospitals were compared and were the same regarding the initiation of oral feeding and mobilisation (ie, stimulating patients to engage in physical activity instead of remaining in bed), preoperative carbohydrate administration, use of drains or nasogastric tubes (not routine), provision of patient information, and discharge criteria. Postoperative antiemetic and analgesic drugs and use of epidural analgesia were not standardised among the participating centres, and the use of an oral bowel preparation was optional. Any confounding effect on study outcomes by these local differences was minimised by stratifying by site. Patients were not allowed to use chewing gum during the study because of possible interference with the primary endpoints.[14] All patients were fasted for oral solids for 6 h and for oral liquids for 2 h before the start of surgery. All patients received 200 mL of oral carbohydrate loading (Nutricia preOp, Nutricia Advanced Medical Nutrition, Zoetermeer, Netherlands)

2 h before the start of surgery. A thoracic epidural catheter was placed in cases of an open procedure unless the patient refused. For laparoscopic procedures, patients did not routinely receive a thoracic epidural catheter for analgesia. The thoracic epidural catheter was infused with an initial bolus of 0·125–0·250 µg/mL of bupivacaine with or without epinephrine (5 µg/mL) and with or without 0·50 µg/mL of sufentanil; the exact quantities were recorded prospectively. Patients without a thoracic epidural catheter received a patient-controlled intravenous analgesic pump with intravenous morphine; alternatively, oral analgesia consisting of acetaminophen and morphine was provided. Continuous postoperative epidural analgesia was achieved with 0·125 µg/mL of bupivacaine and 0·1 µg/mL of sufentanil at 6–12 mL/h. The epidural catheter was removed on postoperative day 3. All patients received a Bair Hugger (3M, St Paul, MN, USA) for temperature control. In cases of expected severe blood loss, a Cell Saver (Haemonetics, Braintree, MA, USA) was readily available. Since perioperative nutrition is a novel principle with a possible risk of aspiration pneumonia, the use of rapid-sequence induction was left to the discretion of the attending anaesthesiologist. After induction of anaesthesia, all patients received a nasogastric tube through which any residual gastric contents were aspirated and quantified. The residual gastric volumes were aspirated via a nasogastric tube and quantified directly after the induction of anaesthesia. The nasogastric tube was removed at the end of the surgical procedure. All patients underwent elective colorectal surgery with creation of a primary anastomosis. Intraoperative radiotherapy was done in some patients with locally advanced rectal cancer; this decision was made by a multidisciplinary team. A deviating transverse colostomy was created in patients with a low anastomosis close to the anal verge.

Follow-up was done until 90 days after surgical resection. All exclusions, serious adverse events, and cases of postoperative ileus and anastomotic leakage were recorded before any analyses and without knowledge of the treatment allocation. Analyses were done after verification that the outcome measures met the definition stated in the original protocol. The randomisation code was broken on March 23, 2017. After finishing the study, all of the used tube sets were checked for possible allocation errors, by flushing the tubes to check whether the nutrition was actually led to the correct branch for each case.

Outcomes

All outcomes were registered on a daily basis. The primary endpoint was postoperative ileus. Secondary outcomes included anastomotic leakage; aspiration pneumonia; preoperative gastric volumes; time to functional recovery; length of hospital stay, calculated as days from the day of surgery; the need for additional surgical, radiological or endoscopic interventions; intensive care unit admission (and length of intensive care unit stay); postoperative inflammatory response; and surgical complications according to the Clavien-Dindo classification.[16] Additional secondary outcomes were measures of intestinal barrier function and local inflammation in the gut, composition of faecal microbiome, quality of life, and cost-effectiveness ratios. These outcomes will be presented in an independent report.

Postoperative ileus was defined as proposed by Vather and colleagues[17] and classified as early, prolonged, or late. Briefly, early postoperative ileus was defined as absence of flatus or stool passage and inability to tolerate a regular oral diet between surgery and postoperative day 4. Prolonged postoperative ileus was defined as at least two of the following criteria on or after postoperative day 4 in patients with early postoperative ileus: nausea or vomiting, inability to tolerate a regular oral diet for the last two meals, absence of flatus and stool for the last 24 h, or radiological confirmation. Late postoperative ileus was defined as the initial development of symptoms of postoperative ileus (absence of flatus or stool passage and inability to tolerate an oral diet) after postoperative day 4. Patients were instructed to register presence of nausea or vomiting, passage of flatus and defecation, and consumption of a regular oral diet in a diary daily. Exact times of first onset of these events were recorded, and the nursing staff or local investigators checked the completion of diary registration on a daily basis. Two researchers analysed the diaries after discharge but before unmasking to establish whether patients had developed early, prolonged, or late ileus.

Anastomotic leakage was diagnosed by means of radiological examination (perianastomotic presence of an abscess, or free air or fluids) or visualised during reoperation, or both. Pneumonia was defined as presence of a pulmonary infiltrate on a radiograph combined with either fever or a rise in inflammatory parameters, corresponding to a revised Uniform Pneumonia Score of 2 or higher.[18] Functional recovery was defined as postoperative patients not receiving intravenous fluid who have adequate pain control, restoration of independent mobility, sufficient caloric intake, and no signs of active infection.[19]

To further assess gastrointestinal motility, gastric emptying was measured using standardised real-time ultrasonography.[20] After a period of nil-by-mouth of at least 2 h in the afternoon of postoperative day 2, patients were offered a standardised meal consisting of 150 mL of liquid and one slice of toast with a topping of their choice.Ultrasound measurements of the longitudinal (D_1) and anteroposterior (D_2) diameters of the gastric antrum were done three times immediately before the meal and, in patients who could completely consume the standardised meal, at 15 and 90 min after the meal.

The antral area (A) was calculated from the mean diameters using the following formula at each timepoint:

$$A = \frac{\pi \times \text{mean}\,(D_1) \times \text{mean}\,(D_2)}{4}$$

The decrease in the gastric antral area, or the gastric emptying rate (GER), was calculated as follows:

$$\text{GER} = \frac{A_{15\text{min}} - A_{90\text{min}}}{A_{15\text{min}}} \times 100$$

To determine the postoperative inflammatory response, we measured plasma C-reactive protein concentrations using an immunoturbidimetric assay (Roche/Hitachi cobas c system, Roche, Mannheim, Germany) as part of routine clinical care on postoperative days 1–4.

Surgical complications were defined as any deviation of the normal postoperative course and were graded according to the Clavien-Dindo classification of surgical complications.[21]

Statistical analysis

Although postoperative ileus was the primary outcome, the sample size was calculated with a power analysis to show an effect on both postoperative ileus and anastomotic leakage because of the clinical relevance of anastomotic leakage. The sample size was calculated based on previous studies by our group.[4,14] For postoperative ileus, a mean incidence of 40% and a reduction of 48% through enteral nutrition or sham-feeding were previously reported.[4,14] Using a power of 0·8 and an alpha of 0·05, 91 patients were needed per group. For anastomotic leakage, our previous data showed a mean incidence of 13% and a reduction of 4% through enteral nutrition or sham-feeding.[4,14] Using a power of 0·8 and a dropout percentage of 5%, 140 patients were needed per group. 140 patients per group were ultimately included to ensure that both the primary endpoint (postoperative ileus) and the most clinically important secondary endpoint (anastomotic leakage) were adequately powered.

All analyses were done according to the intention-to-treat approach regardless of adherence to the study protocol, although patients who were found to meet one or more exclusion criteria after randomisation were excluded from analyses. Subgroup analyses were done according to the stratification parameters. Categorical variables are presented as n (%) and were compared between the groups using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables are presented as the mean (SD) or median (IQR) and were compared between the groups using the independent Student's t test or Mann-Whitney U test, as appropriate. A two-tailed p value less than 0·05 was deemed significant. Treatment effects are reported as risk ratios (RRs) or estimated mean differences with corresponding 95% CIs. All statistical analyses were done with SPSS (version 22).

This trial is registered with ClinicalTrials.gov, number NCT02175979, and trialregister.nl, number NTR4670.

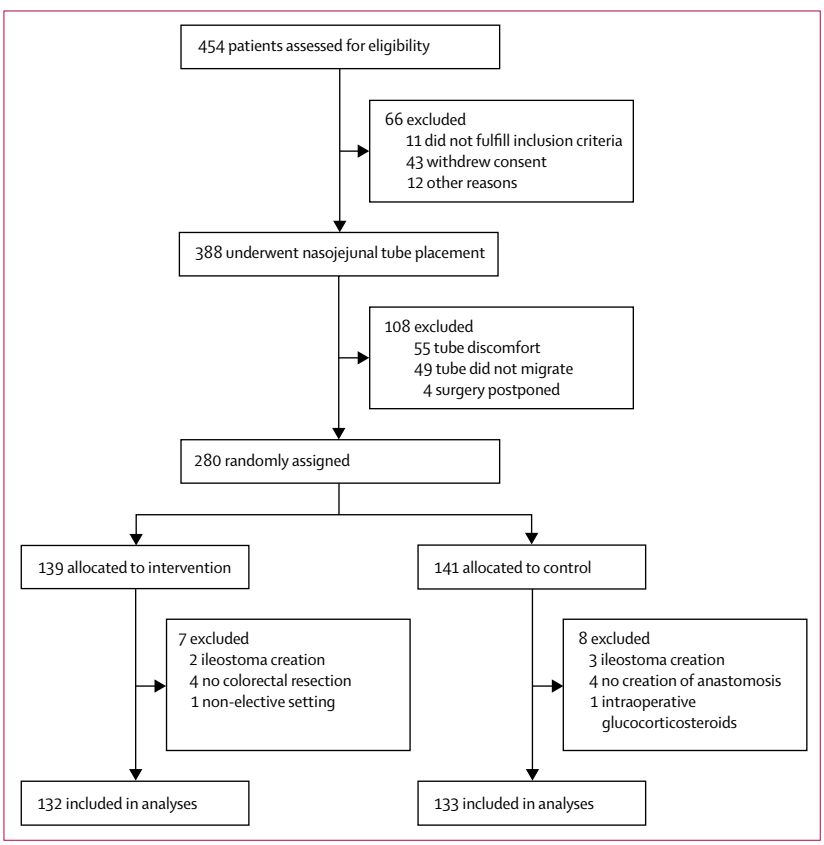

Figure: **Trial profile**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

From July 28, 2014, to Feb 20, 2017, 454 patients were deemed eligible for inclusion (figure). 66 patients were excluded before admission to the surgical wards, mainly because they withdrew consent or were not eligible for study participation (eg, an indication for peri-operative glucocorticosteroids or development of an intestinal obstruction needing prompt surgery). Another 108 patients were excluded upon admission to the ward but before randomisation, mainly because of discomfort of the nasojejunal tube or the prepyloric position of the nasojejunal tube on repeated x-ray. 280 patients were randomly assigned to receive perioperative lipid-enriched enteral tube feeding (intervention group, n=139) or standard care (control group, n=141). There were no allocation errors. Protocol violations occurred in nine

patients in the intervention group, either because of technical problems (eg, tube dislocation) or an accidental late start or premature cessation of the feeding pump. Similar problems occurred in the control group but did not result in protocol violations, because these patients were already allocated to receive no perioperative nutrition. In four patients in the control group a technical issue with the black box resulted in unmasking. No patients were excluded from the analysis because of protocol violations.

15 patients were excluded after randomisation for fulfilling one or more of the exclusion criteria. In five patients, a deviating ileostomy was created for technical reasons, and intraoperative findings in eight patients prohibited colorectal resection or anastomosis (eg, peritoneal carcinomatosis or a dubious vascular supply to the anastomotic segment). One patient in the control group received intraoperative glucocorticosteroids, and one patient in the intervention group deteriorated clinically because of a previously unrecognised intestinal obstruction the night before surgery and underwent surgery in a non-elective setting. Thus, 132 patients in the intervention group and 133 in the control group were included in the analyses. Table 1 summarises demographics and baseline characteristics, which were well matched between the two study groups. We noted slight differences between groups in distribution of ASA grades; however, correction for ASA grade revealed no effect on the outcomes (data not shown). Colorectal malignancy was the indication for surgical resection in 245 (92%) of 265 patients; these patients were equally distributed between the groups based on the TNM (seventh edition) stage. Other indications for colorectal resection were diverticulitis (n=14) endometriosis (n=3), colonic stenosis (n=1), familial adenomatous polyposis (n=1), and irritable bowel disease (n=1). Preoperative oral bowel preparation was given to 60 (45%) patients in the intervention group and to 54 (41%) patients in the control group.

We noted no differences between groups in postoperative ileus occurrence, time to oral intake tolerance, time to first flatus, or time to first defecation (table 2). Although not a prespecified outcome, opioid use did not differ between groups (data not shown). The occurrence of anastomotic leakage and its severity as indicated by the treatment needed were similar between groups (table 2). Incidence of pneumonia was higher in the intervention group than in the control group (ten [8%] *vs* three [2%], RR 1·06, 95% CI 1·00–1·12; p=0·051). The incidences of urinary tract infection (seven [5%] in the intervention group *vs* three [2%] in the control group, RR 1·03, 95% CI 0·98–1·08; p=0·22) and wound infection (nine [7%] *vs* six [5%], 1·03, 0·97–1·09; p=0·42) were similar between groups. We noted no differences between groups in the rate of the highest Clavien-Dindo grade complication or the readmission rate after 30 or 90 days (table 3). Time to functional recovery and length of hospital stay were similar between groups; however, although not significant, the estimated mean differences suggested a longer length of stay and a longer time to functional recovery in the intervention group than in the control group. We did subgroup analyses by surgical approach (open *vs* laparoscopic) and the type of resection (colon *vs* rectum), but found no differences between intervention and control (data not shown).

Two patients in the control group died because of postoperative complications: one patient died on postoperative day 14 after developing septic shock after

	Perioperative nutrition (n=132)	Control (n=133)
Sex		
Male	80 (61%)	78 (59%)
Female	52 (39%)	55 (41%)
Age, years	69 (62–75)	68 (63–74)
Body-mass index, kg/m²	25·8 (23·2–29·0)	26·0 (24·0–29·3)
American Society of Anesthesiologists grade		
I	21 (16%)	24 (18%)
II	96 (73%)	83 (62%)
III	15 (11%)	26 (20%)
Malnutrition Universal Screening Test score		
0	112 (85%)	113 (85%)
1	14 (11%)	11 (8%)
2	3 (2%)	9 (7%)
3	1 (1%)	0
4	2 (2%)	0
Current smoker	14 (11%)	17 (13%)
Diabetes	16 (12%)	22 (17%)
Previous abdominal surgery	49 (37%)	45 (34%)
Neoadjuvant treatment		
Chemotherapy only	0	1 (1%)
Radiotherapy only	5 (4%)	3 (2%)
Chemoradiotherapy	22 (17%)	16 (12%)
Surgical approach		
Laparoscopic	74 (56%)	79 (59%)
Conversion	11 (8%)	15 (11%)
Open	47 (36%)	39 (29%)
Type of operation		
Right hemicolectomy	45 (34%)	49 (37%)
Left hemicolectomy	50 (38%)	51 (38%)
Subtotal colectomy	2 (2%)	3 (2%)
Rectal resection	35 (27%)	30 (23%)
Deviating colostomy	30 (23%)	24 (18%)
Duration of surgery, min	145 (119–185)	150 (120–185)
Intraoperative blood loss, mL	150 (50–300)	100 (50–200)
Thoracic epidural catheter	70 (53%)	66 (50%)
Intraoperative radiotherapy	12 (9%)	8 (6%)

Data are number (%) or median (IQR). Some percentages do not add up to 100 because of rounding.

Table 1: **Demographics and baseline characteristics**

	Perioperative nutrition (n=132)	Control (n=133)	Effect size* (95% CI)	p value
Recovery of bowel function				
Any postoperative ileus	37 (28%)	29 (22%)	1·09 (0·95 to 1·25)	0·24
Early	8 (6%)	7 (5%)	1·01 (0·95 to 1·07)	0·78
Prolonged	19 (14%)	14 (11%)	1·05 (0·95 to 1·15)	0·34
Late	10 (8%)	8 (6%)	1·02 (0·95 to 1·09)	0·61
Time to tolerance of oral diet, h	50 (41–87)	47 (41–71)	16·13 (–7·09 to 39·35)	0·30
Time to first flatus, h	25 (17–45)	23 (13–45)	3·31 (–3·46 to 10·09)	0·23
Time to first defecation, h	48 (24–77)	53 (26–77)	1·12 (–8·02 to 10·26)	0·48
Anastomotic leakage				
Total	12 (9%)	11 (8%)	1·01 (0·94 to 1·09)	0·81
Colon	8/100 (8%)	8/108 (7%)	1·01 (0·93 to 1·09)	0·87
Rectum	4/32 (13%)	3/25 (12%)	1·01 (0·83 to 1·22)	1·00
Treatment needed	..	..	..	0·06
Asymptomatic	0	3 (2%)	..	..
Antibiotics only	6 (5%)	0	..	..
Drainage of abscess	2 (2%)	1 (1%)	..	..
Re-laparotomy	4 (3%)	7 (5%)	..	..

Data are number (%) or median (IQR). *Risk ratios for categorical outcomes and estimated mean differences for continuous outcomes.

***Table 2*: Recovery of bowel function and anastomotic leakage and treatment**

	Perioperative nutrition (n=132)	Control (n=133)	Effect size* (95% CI)	p value
Highest Clavien-Dindo grade†				
No complication	72 (55%)	71 (53%)	1·03 (0·79–1·33)	0·85
I	16 (12%)	22 (17%)	0·95 (0·86–1·05)	0·31
II	29 (22%)	19 (14%)	1·10 (0·98–1·23)	0·10
IIIa	5 (4%)	5 (4%)	1·00 (0·95–1·05)	0·99
IIIb	5 (4%)	8 (6%)	0·98 (0·93–1·03)	0·40
IVa	4 (3%)	6 (5%)	0·99 (0·94–1·03)	0·75
IVb	1 (1%)	0	1·01 (0·99–1·02)	0·50
V	0	2 (2%)	0·99 (0·96–1·01)	0·50
Readmissions within 30 days	11 (8%)	13 (10%)	0·98 (0·91–1·06)	0·68
Readmissions within 90 days	17 (13%)	17 (13%)	1·00 (0·91–1·10)	0·98
Time to functional recovery, days	5·0 (3·0–9·0)	5·0 (3·0–7·0)	1·96 (0·19–3·72)	0·25
Length of stay, days	6·0 (4·0–10·0)	6·0 (4·0–7·8)	2·05 (0·28–3·83)	0·21

Data are number (%) or median (IQR). Some percentages do not add up to 100 because of rounding. *Risk ratios for categorical outcomes and estimated mean differences for continuous outcomes. †The number of complications displayed here is lower than the total number.

***Table 3*: Morbidity and mortality**

anastomotic leakage, and another patient developed fascial dehiscence after undergoing re-laparotomy for an abdominal abscess, which resulted in long-term treatment for an open abdomen and eventual death on postoperative day 54 because of pulmonary oedema. Table 4 summarises details of all Clavien-Dindo complications of grade IIIa or higher. Notably, complications were graded as Clavien-Dindo IIIa or higher in only one of 25 cases of postoperative ileus and two of 13 cases of pneumonia, whereas this occurred in 16 of 23 cases of anastomic leakage. 71 complications (38 intervention and 33 control) occurred at Clavien-Dindo grade I and 75 complications (50 intervention and 25 control) occurred at Clavien-Dindo grade II.

Ultrasonography measurements of the GER on postoperative day 2 were successfully done in 106 patients in the intervention group versus 109 patients in the control group (p=0·73). The reasons the ultrasound measurements were not done (eg, the presence of a colostomy preventing clear visualisation of the pylorus and the patient's inability to consume the standard meal) were equally distributed between groups (data not shown). The percentage decrease in the antral area after a standard meal was similar between groups: 31·4% (IQR 9·8–46·6) in the intervention group versus 32·7% (9·2–45·9) in the control group (estimated mean difference –2·20%, 95% CI –12·61 to 8·22; p=0·76).

Residual gastric volumes were greater in the intervention group than in the control group (median 0·0 mL, IQR 0·0–13·5 *vs* 0·0 mL, 0·0–4·0, estimated mean difference 6·66 mL, 95% CI –0·13 to 13·44; p=0·007). The aspirated gastric contents were clear and did not contain enteral nutrition in any patient. Furthermore, no aspiration was observed clinically. No differences in C-reactive protein concentrations occurred between groups on any postoperative day (appendix p 2).

Discussion

In this international, multicentre, double-blind, randomised controlled trial, perioperative continuous lipid-enriched enteral nutrition did not have beneficial effects on postoperative ileus or surgical complications compared with standard care in patients undergoing colorectal surgery.

Enteral feeding early after colorectal surgery has been associated with reductions in complications and length of stay.[3,5] Furthermore, immunonutrition has been suggested to enhance postoperative recovery by ameliorating the immune response.[22,23] However, the available evidence is heterogeneous in terms of the definitions of the complications studied, patient populations, and timing and composition of the enteral diet, which limit the validity and generalisability of the suggested benefits.[5,24] In our previous experimental and preclinical studies,[10,12] the composition (lipid-rich) and timing (right before and directly after the inciting event) of the enteral diet were essential for establishing the anti-inflammatory effect. The luminal presence of dietary lipids triggers a vagal reflex via peripheral cholecystokinin-1 receptors located on vagal afferents. Via this route, dietary lipids can inhibit both local and systemic inflammation and subsequent postoperative ileus in rodent models.[10,25] However, the current results show that these positive effects are not substantiated in a clinical setting, at least in this study.

Findings from this trial are comparable to those from other studies of colorectal surgery. The overall rates of postoperative ileus (25%) and anastomotic leakage (9%) were consistent with those reported in previous work in which the incidence varied between 2% and 61% for postoperative ileus and between 5% and 50% for anastomotic leakage.[6,7] In the literature, various definitions are used for postoperative ileus, resulting in broad ranges of incidence. For this reason, we used a definition based on objective outcomes that were registered in patient diaries as accurately as possible.[17] Although this process was closely monitored, it remains potentially subject to registration inaccuracies. However, by following a definition based on quantifiable and verifiable variables, we believe postoperative ileus is optimally represented. Most patients underwent laparoscopic procedures, which is the standard approach in modern colorectal surgery, resulting in low mean blood loss volumes. However, inclusion of patients with locally advanced or recurrent cancer diversified the study cohort and accounted for a substantial number of open resections. To minimise confounding, the surgical approach (open *vs* laparoscopic) and the type of resection (colon *vs* rectum) were evenly stratified between the groups. Additionally, all patients were treated according to ERAS protocols, including the use of preoperative carbohydrate loading, which was suggested to attenuate the degree of postoperative insulin resistance.[26] Although the individual effects of preoperative carbohydrate loading or other ERAS components on clinical outcomes or postoperative inflammation are unclear,[27,28] their combined use with laparoscopy seems to substantially reduce the surgical stress response.[29,30] These strategies could have attenuated the surgical stress response to such an extent that the nutritional intervention did not further improve clinical outcomes. Alternatively, the current intervention might not have activated the autonomic nervous system successfully, which was the essential mechanism in our previous preclinical studies.[11,25,31] Intraoperative electrical stimulation of the vagus nerve attenuates inflammation,[32] but further investigations are needed to identify the effect of autonomic nervous system stimulation on postoperative ileus.

In this study, continuous perioperative enteral nutrition was tested in patients undergoing colorectal surgery, although anaesthesia guidelines advocate a period of strict nil-by-mouth to minimise the risk of perioperative aspiration.[13] In a recent study in 33 patients with burns,[33] intraoperative enteral feeding was safe and was not associated with an increased risk of aspiration. Similarly, we observed no aspiration of the gastric contents in the current trial. However, perioperative nutrition was associated with a higher residual gastric volume and a trend toward a higher incidence of pneumonia. Although the overall incidence of pneumonia (5%) was comparable with the incidence reported in other recent studies,[34,35] this finding was concerning and challenged the safety of perioperative enteral feeding.

	Perioperative nutrition (n=132)	Control (n=133)
IIIa	Anastomotic leakage (n=2), bleeding gastric ulcer (n=1), hernia cicatricalis (n=1), haematoma on hand (n=1), haematoma in liver (n=1), postoperative ileus (n=1)	Intraluminal anastomotic bleed (n=2), perianal abscess (n=1), postoperative ileus (n=1), rectus haematoma (n=1)
IIIb	Fascial dehiscence (n=1), trocard hernia (n=1), internal bowel herniation (n=1), adhesion ileus (n=1), anastomotic leakage (n=2)	Anastomotic leakage (n=7), umbilical hernia (n=1), anastomotic stenosis (n=1), trocar hernia (n=1)
IVa	Hypotension (n=1), anastomotic leakage (n=1), bleeding (n=1), parastomal abscess (n=1)	Bilateral pulmonary embolism (n=1), bleeding with asystoly (n=1), morphine intoxication (n=1), pneumonia (n=2), fluid overloading (n=1), respiratory insufficiency (n=1)
IVb	Anastomotic leakage (n=1)	..
V	..	Anastomotic leakage (n=1), fascial dehiscence with respiratory failure (n=1)

Data are number of patients experiencing a complication at each grade.

Table 4: **Clavien-Dindo complications of grade IIIa or higher**

The methodological strengths of this study include the multicentre, double-blind, randomised design; the adequate statistical power for assessing postoperative ileus and anastomotic leakage; and the prospective registration of clearly defined clinical outcomes. However, there are some limitations. First, our results might have been confounded by the absence of standardisation among the participating centres. ERAS protocols were compared before the start of the study, and most ERAS components were applied similarly in all hospitals. However, adherence to the ERAS protocol was not monitored continuously during the trial, leading to possible bias. In particular, the use of epidural analgesia and oral bowel preparation was not standardised for patients undergoing colonic surgery. Although ERAS protocols recommend the use of epidural analgesia and omits bowel preparation, findings from studies in the past few years seem to challenge these practices.[36,37] Regardless, in this study, randomisation was stratified by site, resulting in an even distribution of epidural analgesia and oral bowel preparation between groups. Furthermore, correcting for the use of epidural analgesia and bowel preparation in our data did not alter the interventional effectiveness significantly. Also, the feasibility of the self-migrating nasojejunal tube was limited by the number of patients who did not tolerate tube placement or in whom the tube did not spontaneously migrate post pylorically within 24 h after placement.

Overall, this study represents, to our knowledge, the best available evidence for the use of perioperative lipid-rich enteral nutrition in elective colorectal surgery. Based on our findings, we conclude that perioperative lipid-rich enteral nutrition does not improve clinical outcomes further compared with modern practices in colorectal surgery, including the use of laparoscopy and ERAS protocols.

Contributors
EGP, WAB, and MDPL designed and conceived the study. EGP, BJJS, JN, and CMB collected the data. EGP and BJJS completed case report forms and analysed the data. EGP, BJJS, JN, CMB, JAF, TS, SL, USL, WKGL, GDS, TSdVR, JAW, GAPN, MH, MPB, WJdJ, HJTR, and MDPL interpreted the data. EGP, BJJS, and MDPL wrote the manuscript. All authors critically revised and agreed on the final version of the manuscript and are responsible for its content.

Declaration of interests
EGP, BJJS, and MDPL have received grants from Danone Research, ZonMW, and NutsOhra Fund. MDPL has a patent licence for the nutritional formula used in the intervention group. WAB has a patent issued, WO 2012138224 A1. WJdJ has received grants, personal fees, and non-financial support from Galvani Bioelectronics; grants from Schwabe GmbH; grants and personal fees from Mead Johnson Pediatric Nutrition Institute; and grants and non-financial support from GlaxoSmithKline and Gut-Research BV. All other authors declare no competing interests.

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