Randomized Trial of Perioperative Probiotics Among Patients Undergoing Major Abdominal Operation

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BACKGROUND: We investigated the utility and safety of short-course oral probiotics among patients undergoing major abdominal operations. Perioperative probiotics can decrease length of stay and lower rates of infectious complications. We assessed whether perioperative probiotics decrease major complications among patients undergoing high-risk gastrointestinal operations in a pragmatic randomized trial.

STUDY DESIGN: This double-blind trial randomized 135 patients undergoing elective major gastrointestinal operations to perioperative oral probiotic VSL#3 taken just before operation and twice daily up to 15 total doses (n = 67) or placebo (n = 68). The primary outcomes measure was 30-day composite end point of death, unplanned readmission, or any infection.

RESULTS: Primary end point occurred among 17 patients in the placebo group (25.0%) vs 22 patients in the probiotic group (32.8%; p = 0.315). Thirty-day mortality was 2 (2.9%) in the placebo group compared with 1 (1.5%) in the probiotic group (p = 1.000). The placebo group patients experienced lower 30-day readmission rate (3 of 68 [4.4%]) compared with the probiotic group (11 of 67 [16.4%]; p = 0.022). None of the placebo patients were readmitted for dehydration, but 5 of 11 probiotic group patients (45%; p = 0.049) were readmitted for dehydration as a consequence of diet intolerance and/or diarrhea. There was no difference in 30-day infection rate between the groups (15 or 68 [22%] in the placebo group vs 15 of 67 [22.4%] in the probiotic group; p = 0.963).

CONCLUSIONS: Perioperative use of VSL#3 probiotic did not affect 30-day composite end point of mortality, readmission, and infection rate. A significantly higher readmission rate was observed among those exposed to probiotics. Additional studies remain warranted. (J Am Coll Surg 2019;229: 533−540. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Host-microbiome is susceptible to modulation, including by antibiotics and probiotics, affecting, in turn, many physiologic and disease processes.[1,2] Published evidence supports the role of gut microflora in antibiotic-associated and primary *Clostridium difficile* colitis, chemotherapy-induced enteritis, radiation-induced enteritis, adult respiratory distress syndrome, irritable bowel syndrome, antitumor immunotherapy efficacy, and neoplastic transformation.[1-9]

Several studies including a meta-analysis suggest decreased morbidity, length of postoperative surgical stay, and decreased wound complications among surgical patients treated with perioperative probiotics.[3,4,10-13] Wound complications after liver transplantation were less common among probiotic recipients compared with

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those with selective bowel decontamination, but there was no comparison made with patients without gastrointestinal flora manipulation.[3] Similarly, an improvement in infectious complications was seen among pancreaticoduodenectomy patients treated with postoperative lactobacillus in enteral nutrition in randomized trials.[5,12]

Despite increasing data, a consensus on use of probiotics, prebiotics, and synbiotics in surgical patients is lacking. In addition, concerns about publication bias or selective reporting exist on the effect of probiotics on surgical outcomes. There is sparse yet unequivocal evidence of deleterious effect of probiotics in certain situations, such as among patients with acute pancreatitis.[14]

To further elucidate the potential role of probiotics, we have designed a prospective randomized trial to test a pragmatic and simple intervention in a single institution, assessing whether the rate of perioperative complications in major abdominal elective inpatient general surgical cases can be lowered with the use of a short in-hospital probiotic regimen. Based on earlier studies available at study conception, we formulated our hypothesis that perioperative probiotic intervention is associated with at least a 30% reduction of perioperative complications.

METHODS

This was a single-center prospective randomized parallel-group, double-blind, and placebo-controlled trial assessing the effect of probiotics and recovery from gastrointestinal operation (PROGRESS [Probiotics and recovery from gastrointestinal surgery]; ClinicalTrials.gov ID: NCT01970683) and approved by our local IRB (MMC-DSM-2013-132).

Eligible patients were screened among all elective major gastrointestinal surgical patients cared for by participating surgeons, including all major operations with planned in-hospital stay of more than 2 midnights, with the exception of esophagectomy and total gastrectomy patients for reasons described later. Patients were accrued between January 2015 and February 2017 and followed minimally for 60 days.

Eligible patients were screened by participating surgeons. Main inclusion criterion was elective major abdominal operations with anticipated in-hospital stay more than 2 midnights. Exclusion criteria were current episode of acute pancreatitis; active medication-induced immunosuppression, including systemic corticosteroids, chemotherapy within 3 weeks before operation, immune-modulating agents with transplantation indication, biologic agents for autoimmune disorders (topical chemotherapy or corticosteroids, and chemotherapy applied during operation were allowed); esophagectomy patients and total gastrectomy patients due to their strict nil per os diet within the first 5 to 7 days postoperatively, precluding oral probiotic delivery; patients already taking probiotics; and operations with expected length of stay fewer than 2 midnights.

Probiotic (VSL #3 capsule; Alfasigma) or externally identical-appearing placebo were given orally in preoperative holding area, and twice daily postoperatively for up to 15 doses or until discharge, whichever occurred first. Commercially available high-potency probiotic VSL#3 capsule contains 8 different strains of live lactic acid bacteria with 112.5 billion colony forming units per capsule: *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus.*

Primary outcomes measure was a composite 30-day postsurgical end point including any of the following: death; unscheduled/nonprophylactic antibiotics, drainage procedure, or reoperation (including superficial wound opening due to infection); and readmission within 30 days of the index operation. Planned follow-up operations were not considered as meeting this end point (eg vascular access port for chemotherapy). Secondary outcomes measures were individual components of the composite end point, length of stay, development of *C difficile* colitis, and patient-reported quality of life. Due to logistical reasons, quality of life was measured for surgical oncology patients only, and not among colorectal surgery patients. We used externally validated Functional Assessment of Cancer

Therapy—General 7 questionnaires before operation and during the first postoperative visit.[15,16] Bloating symptomatology was analyzed on ordinal scale from 0 to 4, where 0 represents no bloating (similar to individual items on Functional Assessment of Cancer Therapy—General 7 score). Multivisceral resection was resection of at least 2 named organs except omentum or appendix, and distal pancreatosplenectomy was considered a single-organ resection. Operation was considered minimally invasive if dissection under capnoperitoneum dominated the operative approach. Robotic-assisted and hand-assisted operations were considered minimally invasive.

The study was formulated as a double-blind, placebo-controlled, parallel-arm trial with full concealment. Physicians and clinical nutritionists did not administer or come in contact with study medications, which were administered by in-hospital nursing exclusively. All patients, nurses, evaluators, and physicians were blinded until trial completion. Unblinding before 30 days after operation was allowed on specific request by protocol and occurred in a single instance at physician's request (Fig. 1). Pharmacy recorded number of dispensed medications and treatment duration.

Unstratified 1:1 randomization in blocks of 4 was performed by the inpatient research pharmacy. A power calculation was based on weighted average of infective complications in 3 hepatobiliary-pancreatic trials, demonstrating a 30% absolute risk reduction comparing

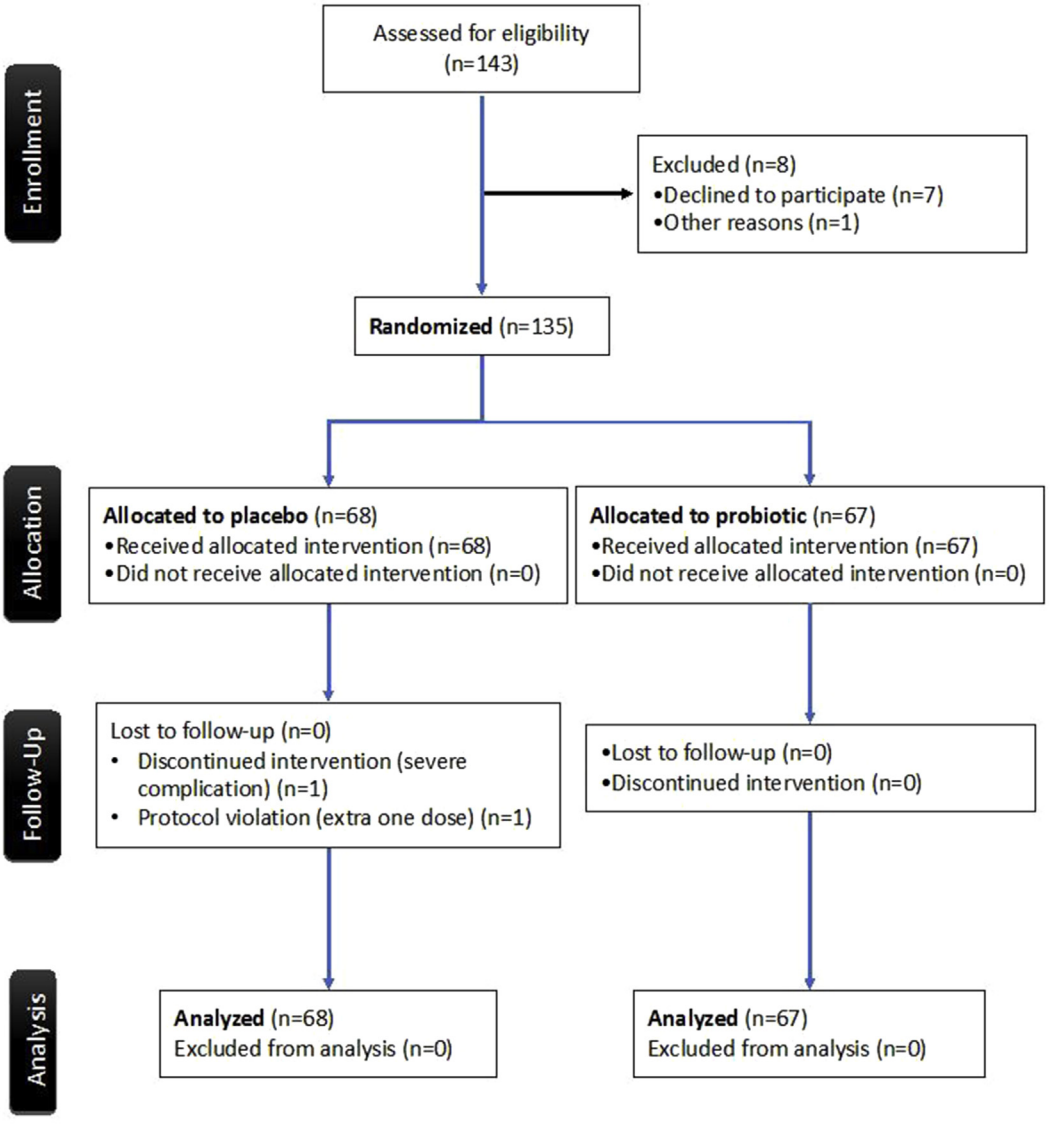

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

Table 1. Characteristics of Study Population

Characteristic	Total	Placebo	Probiotic	p Value
n	135	68	67	0.440
Female, n (%)	69 (51)	31 (45)	35 (52)	
Age, y				0.659
Mean ± SD	62.5 ± 12.1	63.1 ± 11.7	62.0 ± 12.6	
Median	61.6	61.1	61.3	
Minimum	29.4	29.4	33.0	
Maximum	85.8	85.8	83.5	
American Society of Anesthesiologists physical status class				0.320
2	58	31	27	
3	75	37	38	
4	2	0	2	
BMI, kg/m^2				0.609
Mean ± SD	28.7 ± 6.5	28.6 ± 6.9	28.8 ± 6.2	
Median	27.5	27.2	27.5	
Minimum	16.3	16.7	16.3	
Maximum	48.8	48.2	48.8	
Charlson Comorbidity Index (no age adjustment)				0.374
Mean ± SD	2.8 ± 2.5	2.5 ± 2.1	3.1 ± 2.9	
Median	2	2	3	
Minimum	0	0	0	
Maximum	14	9	14	
Smoking status, n (%)				0.869
Current smoker	20 (14.8)	9 (13.3)	11 (16.4)	
Former smoker	56 (41.5)	29 (42.6)	27 (40.3)	
Never smoker	59 (43.7)	30 (44.1)	29 (43.3)	
Preoperative serum albumin, g/dL				0.0169
Mean ± SD	3.8 ± 0.5	3.9 ± 0.4	3.6 ± 0.5	
Median	3.9	4.1	3.7	
Minimum	2.3	2.5	2.3	
Maximum	4.8	4.8	4.5	
Preoperative hemoglobin, g/dL				0.168
Mean ± SD	12.4 ± 2.0	12.7 ± 2.1	12.3 ± 2.0	
Median	12.5	12.8	12.4	
Minimum	7.3	8.2	7.3	
Maximum	17.7	17.1	17.7	
Patient with malignancy, n (%)	85 (63.0)	40 (58.8)	45 (67.2)	0.316
Length of stay, d				0.421
Mean ± SD	5.8 ± 7.6	5.2 ± 5.9	6.3 ± 9.1	
Median	3.3	3.2	3.4	
Minimum*	0.48	0.77	0.48	
Maximum	63.2	36.1	63.1	

*Expected length of stay was ≥2 midnights per inclusion criteria, but a few patients experienced a better than expected course and were discharged after a single night in hospital.

probiotics with control groups.[5,12,17] Pooled data of these studies indicate that the failure rate among controls is 40% (death 1%, readmission 13%, infection rate 8%, and unscheduled antibiotics 18%). Assuming relative risk of failure for experimental subjects relative to controls is 0.7 (30% reduction in risk), we needed to study 81 experimental subjects and 81 control subjects to be able to reject the null hypothesis that this relative risk equals

Table 2. Operative Characteristics

Characteristic	Total	Placebo	Probiotic	p Value
Multivisceral resection, n (%)	25 (18.5)	9 (13.2)	16 (23.9)	0.111
Colonic anastomosis, n (%)	92 (68.1)	50 (73.5)	42 (62.7)	0.176
No. of visceral anastomoses, n (%)				0.160
0	14 (10.4)	5 (7.3)	9 (13.4)	
1	102 (75.5)	57 (83.8)	45 (67.2)	
2	7 (5.2)	2 (2.9)	5 (7.5)	
3	12 (8.9)	4 (5.9)	8 (11.9)	
Proportion of minimally invasive surgery, n (%)	92 (68.1)	51 (75.0)	41 (61.2)	0.085
Operation duration, min				0.484
Mean ± SD	265 ± 118	261 ± 126	269 ± 111	
Median	244	247	237	
Minimum	31	31	70	
Maximum	707	707	549	

Multivisceral resection was resection of at least 2 named organs except omentum or appendix.

1 with probability (power) 0.8 and type I error 0.05. Data are presented as mean ± SD or proportions as appropriate. Proportions are compared by uncorrected chi-square test. Paired comparisons or ordinal data are analyzed by Wilcoxon signed-rank paired test and between-group differences by Mann-Whitney test. Paired *t*-test is used to analyze normally distributed pooled quality of life data represented by Functional Assessment of Cancer Therapy—General 7 score (normality of data was confirmed by Shapiro-Wilk test). Statistical analysis was performed with STATA, version 15 (Stata Corp).

RESULTS

This trial was closed prematurely after the second interim analysis suggested futility. There were 135 patients randomized to placebo (n = 68) or probiotic (n = 67) (Fig. 1). Demographic and clinical characteristics were well-balanced between the groups, except significantly lower albumin level among those with probiotics (Table 1). Patients took on average 7.2 ± 3.1 (median 7) study doses with no difference between the groups (6.6 ± 2.7 vs 7.7 ± 3.5; p = 0.082). Number of obese patients, defined as those with BMI ≥30 kg/m^2, was 26 in each group. Study population included 93 colorectal resections (including 22 rectal resections), 2 combined colon and liver resections, 22 major hepato-biliary-pancreatic cases plus 10 pancreaticoduodenectomies, 4 cytoreductive procedures with hyperthermic intraperitoneal chemotherapy, and 4 other major intra-abdominal procedures (Tables 1 and 2).

Primary end point (mortality, readmission, or infection within 30 days of operation) occurred among 17 patients in the placebo group (25.0%) vs 22 patients in the probiotic group (32.8%; p = 0.315) (Fig. 2). Thirty-day mortality was 2 (2.9%) in the placebo group compared with 1 (1.5%) in the probiotic group (p = 1.000). Placebo group experienced lower 30-day readmission rate (3 of 68 [4.4%]) compared with the probiotic group (11 of 67 [16.4%]; p = 0.022). This significant difference in readmission was persistent at 60 days after the procedure (placebo group 4 of 68 [5.9%] vs probiotic group 13 of 67 [19.4%]; p = 0.018). In an ad-hoc analysis, a univariate logistic regression model to control for preoperative albumin did not predict the primary end point (p = 0.104) and in a separate model preoperative albumin level did not predict 30-day (p = 0.395) or 60-day readmission (p = 0.256).

We performed ad-hoc sensitivity analysis stratified on colorectal vs noncolorectal operations and identified no differences: among colorectal surgery patients (n = 95) there were 10 of 40 (25%) meeting primary end point compared with 10 of 55 (18.2%) in the placebo group (p = 0.421). Among patients with noncolorectal abdominal operation (n = 40; of these 32 were major hepatopancreatic procedures) primary end point was observed among 12 of 27 (44.4%) patients on probiotic compared with 7 of 13 (53.8%) patients in the placebo group (p = 0.577).

Among readmitted patients from the placebo group, there were 2 in-hospital readmissions and 1 unplanned emergency department visit resulting in continued outpatient care. Among the probiotic group patients, 10 patients experienced unplanned hospital readmission at least once (7 patients once, 3 patients 2 or more times) and an additional 1 patient with unplanned emergency department visit resulting in continued outpatient care. None of the placebo patients were readmitted for dehydration, but 5 of 11 probiotic group patients (45%; p = 0.049) were readmitted for dehydration resulting from diet intolerance or diarrhea. *C difficile* colitis was

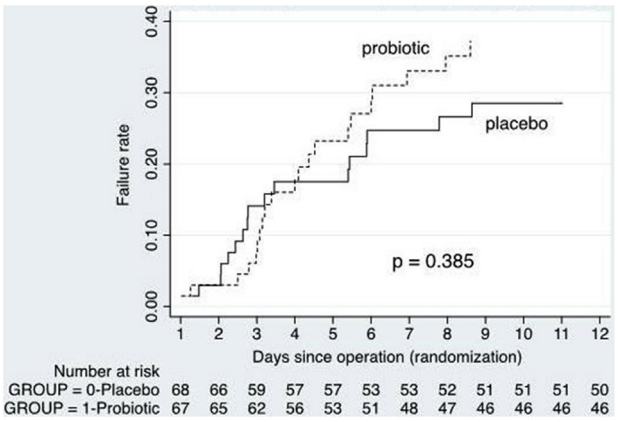

Figure 2. Nelson-Aalen cumulative hazard estimates. Time until development of the primary end point (composite outcome of 30-day occurrence of death, readmission, or infection). Outcomes were tracked for 30 days. All but 1 event occurred within 12 days and therefore the graph is terminated at 12 days for better visualization.

confirmed based on fecal polymerase chain reaction test in 1 patient in each group ($p = 0.992$).

There was no difference in 30-day initiation of unplanned/therapeutic antibiotics between the groups (15 of 68 [22%] in placebo vs 15 of 67 [22.4%] in probiotic group; $p = 0.963$). Time until solid diet order was similar between the groups (median 2 days in each group; $p = 0.141$). Quality of life was measured among surgical oncology patients only ($n = 42$). Patients in the placebo group experienced an expected decline in measured quality of life assessed during the first postoperative clinic visit (21.6 ± 3.9 vs 18.0 ± 6.3 points; $p = 0.019$). Those exposed to probiotics did not experience any such decline in quality of life measurement (16.3 ± 5.1 points vs 17.1 ± 5.0 points; $p = 0.327$, see Fig. 3 and eFig. 1). No significant difference between preoperative and first postoperative clinic-based measurement was identified for bloating (placebo group: preoperatively 0.5 ± 0.9 vs 0.9 ± 1.3 points postoperatively; $p = 0.239$; probiotic group: preoperatively 1.1 ± 1.3 vs 1.3 ± 1.2 points postoperatively; $p = 0.410$).

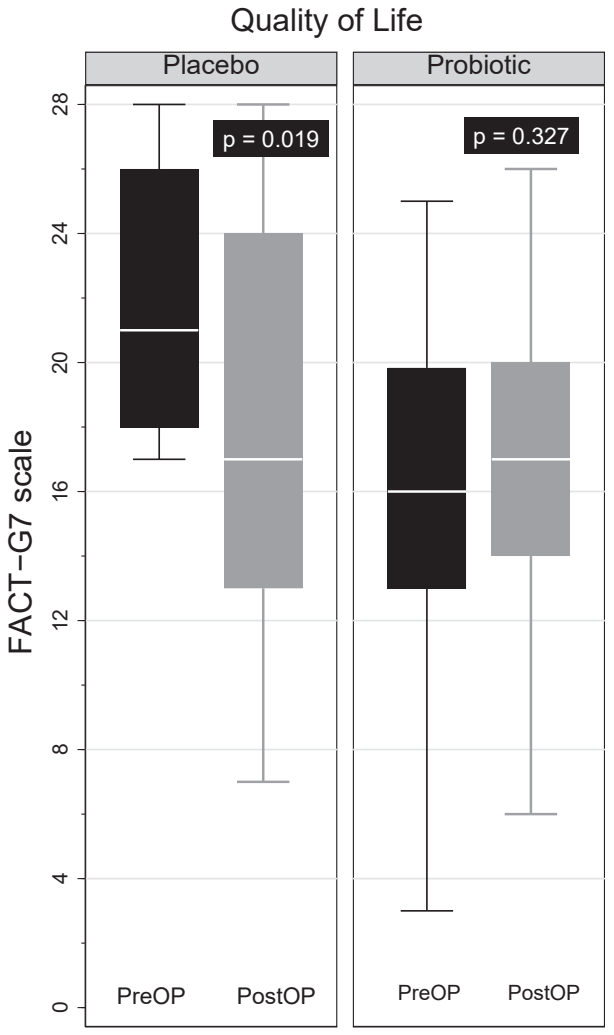

Figure 3. Quality of life reported by patients on Functional Assessment of Cancer Therapy-General 7 (FACT-G7) scale during preoperative office visit (black) and after the operation during the first office visit (gray). Reduction of quality of life was mitigated among patients in probiotic group.

DISCUSSION

Microbiome is now understood to influence a variety of both pathologic conditions and normal functions, and its manipulation might improve certain outcomes of patients undergoing gastrointestinal operations.[4,18,19] Probiotics can influence a host's microbiome and have been shown to significantly decrease infection rates in some surgical trials.[5,13,17,20,21] In addition, co-administration of probiotics during antibiotic therapy among adult patients with nonsurgical infection decreases rates of *C difficile* colitis.[7]

We elected to conduct this study after reviewing earlier trials suggesting marked decreases in surgical site infections and length of stay.[5,17,20,22] Since the current trial was designed and initiated, an increased variability in reported surgical outcomes in trials incorporating pre- and probiotics became apparent subsequent to a negative trial among colorectal surgery patients[23] being published. Nevertheless, this study remains one of the largest double-blind, concurrent-arm, fully concealed, randomized surgical trials of perioperative probiotics. Although only a few larger studies are reported on probiotics in surgery, many were either

nonblinded,[23] too small,[14,24] or without report of randomization concealment.[13]

Contrary to other studies[5,13,17,20,21] and a metanalysis,[4] we have not identified improved outcomes among patients taking a short perioperative course of commercially available probiotics compared with placebo. There have been other randomized trials demonstrating no improvement in infection rates or other postoperative complications in colorectal surgical patients treated with probiotics.[8,23] Additionally, increased mortality associated with use of probiotics was observed in a randomized trial among patients with severe acute pancreatitis.[14] One must note that the interpretation of probiotic or prebiotic studies is challenged by reporting variability of infectious complications, with some studies reporting all infectious complications, and others focusing on surgical site infections only.

Probiotics are considered generally safe in immunocompetent patients and undesired side effects of probiotics are rare, although possibly underreported. The higher readmission rate reported herein, however, adds to a limited number of studies pointing to possible harm associated with probiotics.[2,8,14] On the other hand, and contrary to a small historical report, we did not observe increased patient-reported bloating among those taking probiotics.[8] Probiotics are associated with significantly improved quality of life in certain chronic abdominal conditions,[9] but quality of life was not studied perioperatively previously. Due to logistical reasons, we were limited to evaluating quality of life among noncolorectal patients only, but interestingly enough we did observe mitigation of postoperative decline in quality of life among probiotic patients.

This trial population consists of patients with a broad spectrum of complex abdominal operations, which can be viewed as both a strength (pragmatic generalizability) and a limitation due to inherent variability. Yet, benefits of probiotics were documented in randomized trials among patients with pancreaticoduodenectomy,[5] hepatectomy,[17,22] and colorectal resections.[20,21] Therefore, we believe it is reasonable to consider a broad-spectrum patient cohort for this study.

Perhaps the largest limitation of the current study is the observed imbalance between the groups in baseline serum albumin level and quality of life. Randomization imbalance can occur haphazardly and indeed similar imbalances were observed in other published surgical trials.[25,26] Although between-group baseline difference in the mean serum albumin levels is only 0.3 g/L, it is nevertheless statistically significant and, consequently, might have influenced the outcomes. It remains reassuring that unplanned logistic regression analyses do not suggest this imbalance affected study outcomes. Our choice of very short preoperative treatment differs from most other studies, although several trials that reported probiotic-associated clinical benefit similarly used a rather short preoperative treatment course.[20,21,23] To assure medication compliance, we chose a practical approach of in-hospital administered treatment.

CONCLUSIONS

Perioperative use of VSL#3 probiotic did not result in change of 30-day composite end point of mortality, readmission, and infection rate. Unexpectedly, we observed a significantly higher early readmission rate among those treated with probiotics. Additional studies remain warranted.

Author Contributions

Study conception and design: Franko
Acquisition of data: Franko, Raman, Krishnan, Frankova, Tee, Brahmbhatt, Goldman
Analysis and interpretation of data: Franko, Raman, Krishnan, Frankova, Tee, Brahmbhatt, Goldman, Weigel
Drafting of manuscript: Franko, Raman, Krishnan, Frankova, Tee, Brahmbhatt, Goldman, Weigel
Critical revision: Franko, Raman, Krishnan, Frankova, Tee, Brahmbhatt, Goldman, Weigel

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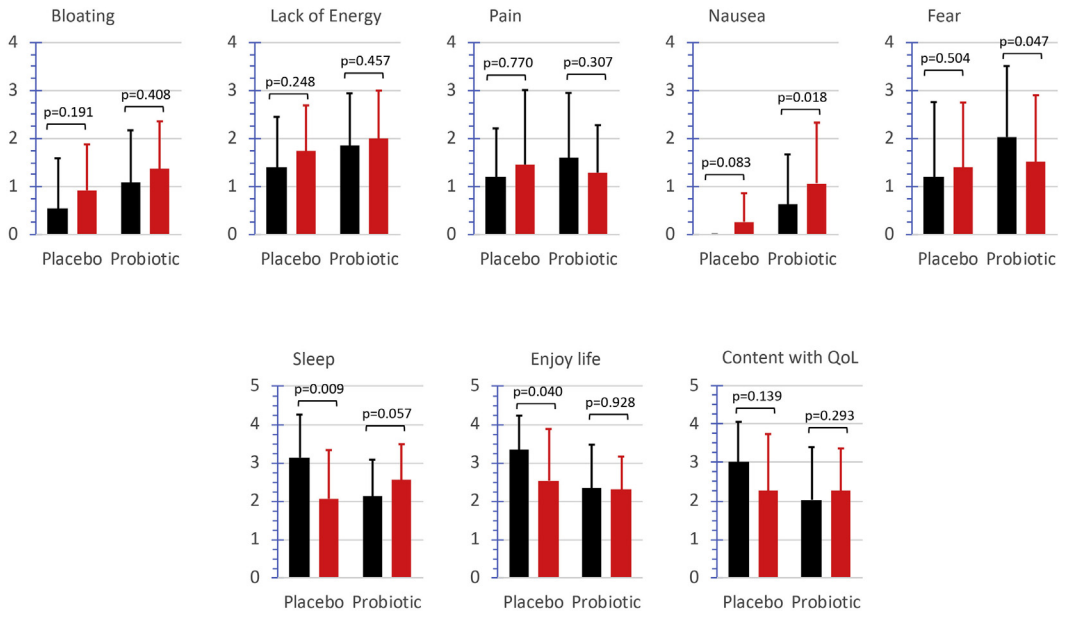

eFigure 1. Detailed analysis of quality of life (QoL) by individual Functional Assessment of Cancer Therapy-General 7 (FACT-G7) questions. Bloating subscale is not a part of FACT-G7, but uses the same ordinal scale 0 through 4. Lack of energy (GP1), pain (GP2), nausea (GP3), and emotional well-being (GE6) labeled as "fear" are in the upper row. Higher values represent worse QoL. Functional well-being subscale items sleep (GF5), enjoyment of life (GF3), and content with one's QoL (GF7) are in bottom row. Higher values represent better QoL. The p values compare before and after procedure QoL items using Wilcoxon matched-pair signed-rank test.

eDocument 1. International Committee of Medical Journal Editors Data Sharing Statement

Question	Answer
Will individual data be available?	No
What data in particular will be shared?	NA
What other documents will be available	NA
When will data be available?	NA
With whom?	NA
For what types of analyses	NA
By what mechanism?	NA

NA, not applicable.