Digestive and Liver Disease 46 (2014) 1126–1132

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Effects of 12 weeks of probiotic supplementation on quality of life in colorectal cancer survivors: A double-blind, randomized, placebo-controlled trial

Jee-Yon Lee[a], Sang-Hui Chu[b], Justin Y. Jeon[c], Mi-Kyung Lee[c], Ji-Hye Park[c], Duk-Chul Lee[a], Ji-Won Lee[a,*], Nam-Kyu Kim[d,**]

[a] Department of Family Medicine, Yonsei University, College of Medicine, Republic of Korea
[b] Department of Clinical Nursing Science, Yonsei University, College of Nursing, Nursing Policy Research Institute, Biobehavioural Research Center, Republic of Korea
[c] Department of Sport and Leisure Studies, Sports Medicine Laboratory, Yonsei University, Republic of Korea
[d] Department of General Surgery, Yonsei University College of Medicine, Republic of Korea

ARTICLE INFO

Article history:
Received 5 June 2014
Accepted 14 September 2014
Available online 23 October 2014

Keywords:
Bowel symptoms
Cancer survivors
Colorectal cancer
Probiotics

ABSTRACT

Background: Probiotics may help resolve bowel symptoms and improve quality of life. We investigated the effects of 12 weeks of probiotics administration in colorectal cancer patients.
Methods: We conducted a double-blind, randomized, placebo-controlled trial. The participants took probiotics (*Lacidofil*) or placebo twice a day for 12 weeks. The cancer-related quality of life (FACT), patient's health-9 (PHQ-9), and bowel symptom questionnaires were completed by each participant.
Results: We obtained data for 32 participants in the placebo group and 28 participants in the probiotics group. The mean ages of total participants were 56.18 ± 8.86 years and 58.3% were male. Administration of probiotics significantly decreased the proportion of patients suffering from irritable bowel symptoms (0 week vs. 12 week; 67.9% vs. 45.7%, $p = 0.03$), improved colorectal cancer-related FACT (baseline vs. 12 weeks: 19.79 ± 4.66 vs. 21.18 ± 3.67, $p = 0.04$) and fatigue-related FACT (baseline vs. 12 weeks: 43.00 (36.50–45.50) vs. 44.50 (38.50–49.00), $p = 0.02$) and PHQ-9 scores (0 weeks vs. 12 weeks; 3.00 (0–8.00) vs. 1.00 (0–3.00), $p = 0.01$). We found significant differences in changes of the proportion of patients with bowel symptoms ($p < 0.05$), functional well-being scores ($p = 0.04$) and cancer-related FACT scores ($p = 0.04$) between the two groups.
Conclusion: Probiotics improved bowel symptoms and quality of life in colorectal cancer survivors.

1. Introduction

Colorectal cancer (CRC) is one of the most common cancers, and its prevalence is increasing in Asian countries [1]. However, because of the development of treatment modalities, including surgery, radiation therapy, and chemotherapy, the 5-year survival rate for CRC is increasing steadily [2]. Therefore, long-term care of CRC survivors and acute treatment of CRC are extremely important. CRC survivors who have completed treatment are known to suffer from various kinds of chronic symptoms. Previous studies have reported that many CRC patients suffer from chronic bowel symptoms that affect quality of life significantly [3–5]. Although the precise mechanism is unknown, shortening of bowel transit time and bowel mucosal injury following bowel resection and chemo-radiation therapy could cause bowel symptoms, including diarrhoea and gas formation [6–8]. Furthermore, an imbalance of intestinal flora is thought to be related to bowel dysfunction in CRC after surgery. Decreased levels of normal flora and increased levels of pathogenic bacteria have been reported after surgery in CRC patients [9].

Probiotics, food supplements of live microorganisms that affect the intestinal microbial balance in the host, are known to have many beneficial effects on human health. Previous studies have reported positive effects of probiotics on bowel diseases, including infant diarrhoea [10,11], inflammatory bowel disease [12], and irritable bowel syndrome (IBS) [13]. Particularly, the positive effects

* Corresponding author at: Department of Family Medicine, Yonsei University College of Medicine, Yonsei University, 250 Seongsan-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea. Tel.: +82 2 2228 2330; fax: +82 2 362 2473.
** Corresponding author at: Department of Surgery, Yonsei University College of Medicine, Yonsei University, 250 Seongsan-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea. Tel.: +82 2 2228 2117; fax: +82 2 362 2473.
E-mail addresses: indi5645@yuhs.ac (J.-W. Lee), namkyuk@yuhs.ac (N.-K. Kim).

http://dx.doi.org/10.1016/j.dld.2014.09.004
1590-8658/

of probiotics on IBS have been well studied, and several meta-analyses have concluded that probiotics containing specific strains improve the global symptoms of IBS and abdominal pain [13–15]. For example, *Lactobacillus* species, including *L. rhamnosus* GG and *L. acidophilus*, significantly improved the severity and frequency of abdominal pain in IBS patients [16]. Although the precise mechanisms are still unknown, probiotics are considered to improve IBS symptoms by promoting a restored balance of the gastrointestinal microbiota [17], reducing inflammation [18], and increasing mucosal immune regulation [19].

Because disruption of gut microbial balance may aggravate bowel symptoms in CRC, supplementation with probiotics may help resolve bowel symptoms and improve quality of life in CRC patients. Ohigashi et al. [20] have reported that 12 weeks of probiotics intake after CRC surgery reduce bowel symptoms and improve functional outcomes. However, there have been no randomized, controlled studies of these effects. Therefore, we investigated the effect of probiotics supplementation on bowel symptoms and quality of life in CRC patients with a double-blind, placebo-controlled, randomized study.

2. Materials and methods

2.1. Participants

We performed a randomized, placebo-controlled, double-blind study involving patients diagnosed with stage 2 or 3 colorectal cancer aged >20 years who had been performing well and who completed treatments between 6 weeks and 2 years prior. The performance status of the participants was evaluated on the basis of Eastern Cooperative Oncology Group performance scores, with total scores less than 1 indicating good performance. The study population was recruited by advertisement at the Outpatient Clinic of the Department of General Surgery in Severance Hospital. All subjects participated in the study voluntarily, and written informed consent was obtained from each participant. The study complied with the Declaration of Helsinki, and the institutional review board of Yonsei University College of Medicine approved this study (Clinical trial number: KCT0001053).

We excluded volunteers with histories of cancer in other organs. We also excluded patients with colostomies. Volunteers who were consuming yoghourt or other supplementary food that contained probiotics were also excluded. Participants were excluded if they had any of the following complicating conditions: (1) a history of chronic diseases, including coronary artery occlusive disease, stroke, chronic liver disease, or renal disease; (2) antibiotic use; (3) pregnancy or planned pregnancy; (4) abnormal liver function, kidney function, or blood cell counts. Abnormal liver function was defined by serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentrations greater than 100 IU/L. Abnormal kidney function was defined by serum creatinine concentrations greater than 1.7 mg/dL. Abnormal blood cell count was defined by white blood cell (WBC) counts greater than 10,000 cells/L, haemoglobin levels less than 10 mg/dL or platelet counts less than 15,000/mcL or greater than 400,000/mcL. No participants had physical or mental disabilities.

The exclusion of 13 patients based upon the aforementioned criteria resulted in 66 participants included in the study. Participants were randomly assigned to one of two groups, placebo or probiotic, by computer-generated random selection numbers. This randomization procedure resulted in a 1:1 allocation into the probiotic and placebo groups. The randomization procedures were performed by the staff of the Clinical Trial Center in Severance hospital who was blind to the study. During the 12 weeks of administration of probiotics or placebo, a total of 6 participants dropped out. The results of 60 participants (28 in the probiotics group, 32 in the placebo group) were used in the final data analysis (Fig. 1).

2.2. Study design

Between February 2012 and December 2012, a total of 66 CRC survivors were randomly allocated to receive *Lactobacillus* (Lacidofil) or a placebo for 12 weeks. The participants visited the hospital five times, including the initial visit during which they were enrolled and baseline measurements were collected.

On the first visit after the baseline measurement, the participants were provided one bottle containing 6 weeks of pills containing probiotics or the matching placebo. The probiotic preparation (Lacidofil) contained *L. rhamnosus* R0011·*L. acidophilus* R0052 bacterial culture (2×10^9 colony-forming units), maltodextrin, magnesium stearate, and ascorbic acid. The control group received placebo pills composed of maltodextrin, magnesium stearate, and ascorbic acid. The placebo was comparable in texture, taste, and colour to the probiotics. The participants were instructed to take the tablets twice daily with or right after meals and to keep the bottle of tablets in the refrigerator. The participants were forbidden to consume food containing probiotics, including yogurt. Family medicine doctors provided 15-minute lectures about how to properly ingest the pills. Participants could contact the researcher any time with a phone call if they had problems while taking the medications or if they had questions.

The second visit was performed after 6 weeks of administration. The participants were asked to submit the remaining pills. If more than 20% of the pills remained, the participant would be excluded from the final analysis. However, no participant was found to have more than 20% pills remaining. Participants answered questions about side effects of the administration, including bloating, abdominal pain, excessive gas, diarrhoea, and other symptoms. Each group received a new bottle containing the probiotics or placebo for the remaining 6 weeks.

The final visit was performed after the final 6 weeks of administration. Remaining pills were counted in the same fashion.

2.3. Measurements

All participants completed anthropometric measurements and completed questionnaires about health-related lifestyles, underlying diseases, quality of life, and bowel symptoms upon enrolment. After 12 weeks of treatment, participants provided information about quality of life and bowel symptoms through a repeated questionnaire. All of the measurements took place in a comfortable and quiet room by well-trained family medicine doctors who were blind to the group assignment.

2.3.1. Anthropometric measurements

Blood pressure was measured in the sitting position after a 10-minute resting period. Body mass index (BMI) was calculated as weight divided by height squared. Waist circumference was measured at the umbilicus while the participant was standing.

2.3.2. Biochemical analyses

Biochemical analyses were performed as part of the baseline measurements for excluding participants with abnormal laboratory test results. Blood samples were collected after at least an 8-hour overnight fasting period. White blood cell and platelet counts and serum haemoglobin, AST, ALT, creatinine, glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride concentrations were measured using an ADVIA 1650 chemistry system (Siemens Medical Solution, Tarrytown, NY, USA).