News Release

Title

Impact of synbiotics treatment on bacteremia induced during neoadjuvant chemotherapy for esophageal cancer: A randomised controlled trial

Key Points

- We hypothesized that preoperative use of synbiotics contributes to prevention of bacterial translocation and unfavorable events that occur during neoadjuvant chemotherapy for esophageal cancer.
- Administration of synbiotics effectively reduced the incidence of bacteremia, detected with bacterium specific ribosomal RNA-targeted RT-PCR, during chemotherapy. Presence of bacteria in the mesenteric lymph node (MLN) sampled during surgery was reduced. Synbiotics also reduced the incidence of side effects induced by neoadjuvant chemotherapy.
- Neoadjuvant chemotherapy for esophageal cancer may induce bacterial translocation and subsequent bacteremia, which can be prevented by synbiotics administration.

Summary

The aim of this study was to clarify whether neoadjuvant chemotherapy for esophageal cancer induces bacterial translocation and to investigate whether synbiotics treatment can prevent bacterial translocation during chemotherapy and subsequent esophagectomy by performing a randomized controlled study.

Administration of synbiotics effectively reduced the incidence of bacteremia detected with RT-qPCR during chemotherapy. Presence of bacteria in the MLN sampled during surgery was reduced. Synbiotics also reduced the incidence of side effects induced by neoadjuvant chemotherapy, which is consistent with the previous randomized controlled study.

Research Background

Synbiotics is a combination of prebiotics and probiotics. Preoperative administration of synbiotics improves the intestinal microenvironment and decreases the incidence of postoperative infectious complications in hepatectomy with extrahepatic bile duct resection. Preoperative administration of synbiotics also decreases the incidence of bacterial translocation through improvement of intestinal microenvironment, in patients undergoing esophagectomy and pancreatoduodenectomy.

Neoadjuvant chemotherapy is generally performed as a standard treatment for esophageal cancer. Combination therapy using cisplatin and 5-fluorouracil is one of the most common regimens used in patients with advanced esophageal cancer. This regimen, however, strongly affects the gastrointestinal mucosa (which may induce bacterial translocation) and frequently induces fever, nausea, vomiting, stomatitis, and diarrhea.

In this study, patients requiring neoadjuvant chemotherapy for esophageal cancer were randomized to receive synbiotics (synbiotics group) or no synbiotics (control group) during chemotherapy.

Blood and fecal samples were taken before and after every chemotherapy cycle, and 1 day before surgery. Mesenteric lymph nodes (MLNs) were harvested at laparotomy (MLN-1) and after resection of the tumor (MLN-2). Bacteria in each sample were detected. Fecal microbiota and organic acid concentrations were also determined. The primary endpoint was the detection of bacteria in the blood samples, as well as the incidence of side effects during chemotherapy. The secondary endpoint was the detection rate of bacteria in the MLN samples collected during surgery.

Research Results

The study recruited a total of 42 patients (22 in the control group, 20 in the synbiotics group). Bacteria were detected in 16 of 101 blood samples in the control group, whereas those were detected only 2 of 100 blood samples in the synbiotics group ($p<0.001$) during neoadjuvant chemotherapy (Figure 1).

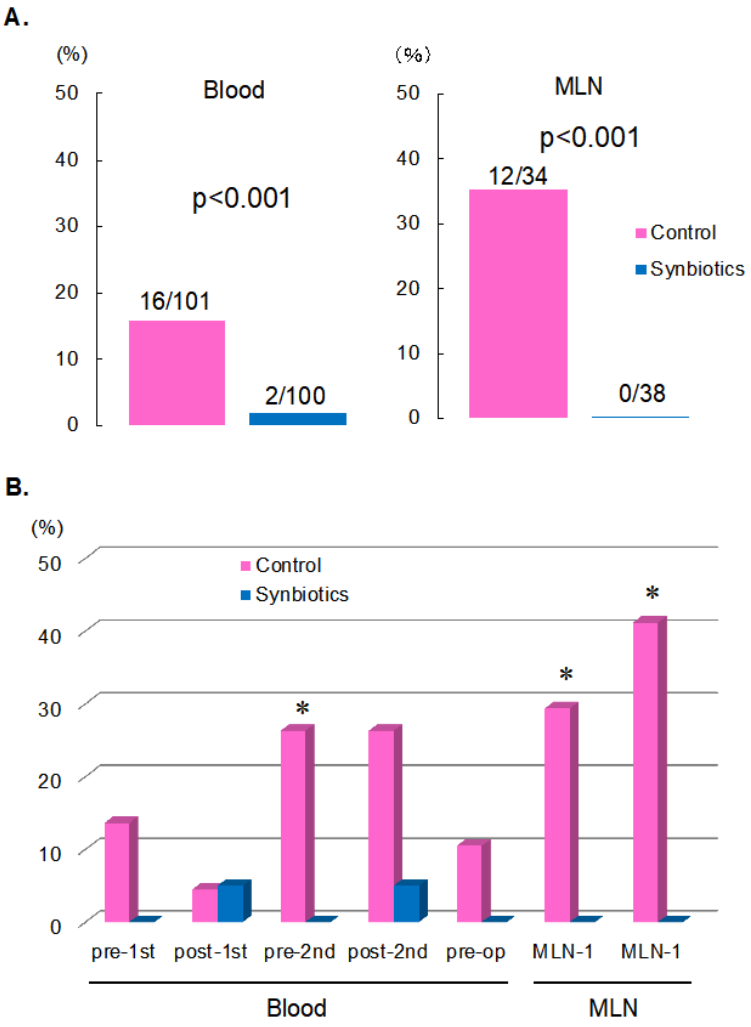

Figure 1.

The detection rate of bacteria in total blood and MLN samples (A) and that in each time point (B). Blood samples were collected before starting the first chemotherapy (pre-1st), on day 7 after starting the first cycle (post-1st), before starting the second cycle (pre-2nd), on day 7 after starting the second cycle (post-2nd), and 1 day before surgery (pre-op). MLN samples harvested during surgery at laparotomy (MLN-1) and after tumor resection (MLN-2).
*$p < 0.05$ vs. synbiotics group.

The incidence of gastrointestinal toxicity was significantly higher in the control group compared to the synbiotics group ($p = 0.022$).

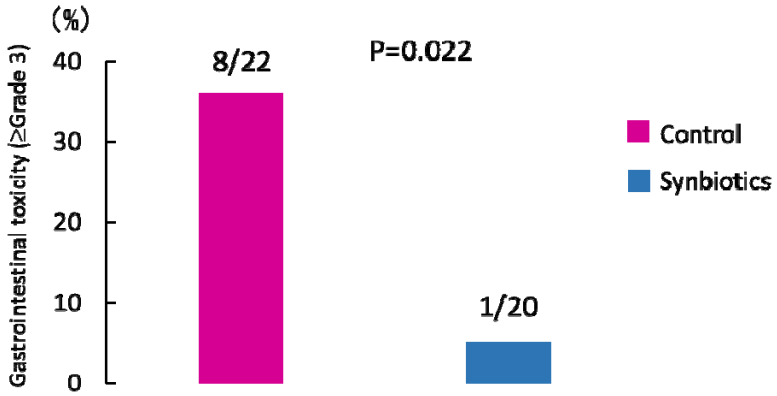

Figure 2.
The rate of severe (≥Grade 3) gastrointestinal toxicity

In the synbiotics group, a high number (~10^8 cells/g feces) of *Bifidobacterium breve* strain Yakult and *Lacticaseibacillus paracasei* strain Shirota, which were administered as probiotics, were detected in the feces throughout the whole course of chemotherapy in all patients (Figure 3). However, these bacteria were scarcely detected in the control group.

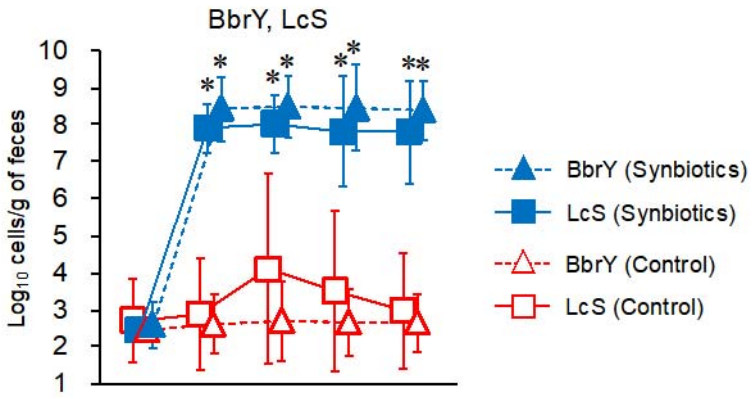

Figure 3.
Effect of synbiotics treatment on fecal microbiota. BbrY, *Bifidobacterium breve* strain Yakult;

LcS, *Lacticaseibacillus paracasei* strain Shirota.
*p < 0.05 vs. control group.

The fecal concentrations of total organic acids were significantly higher in the synbiotics group compared to the control group at all time points during chemotherapy. In particular, the concentrations of acetic acid, which is the most predominant organic acid in the feces and is important for preserving intestinal mucosa integrity, were maintained at a high level in the synbiotics group compared to the control group (Figure 4A). Although the fecal pH gradually increased during chemotherapy in the control group, it was maintained at a lower level in the synbiotics group (Figure 4B).

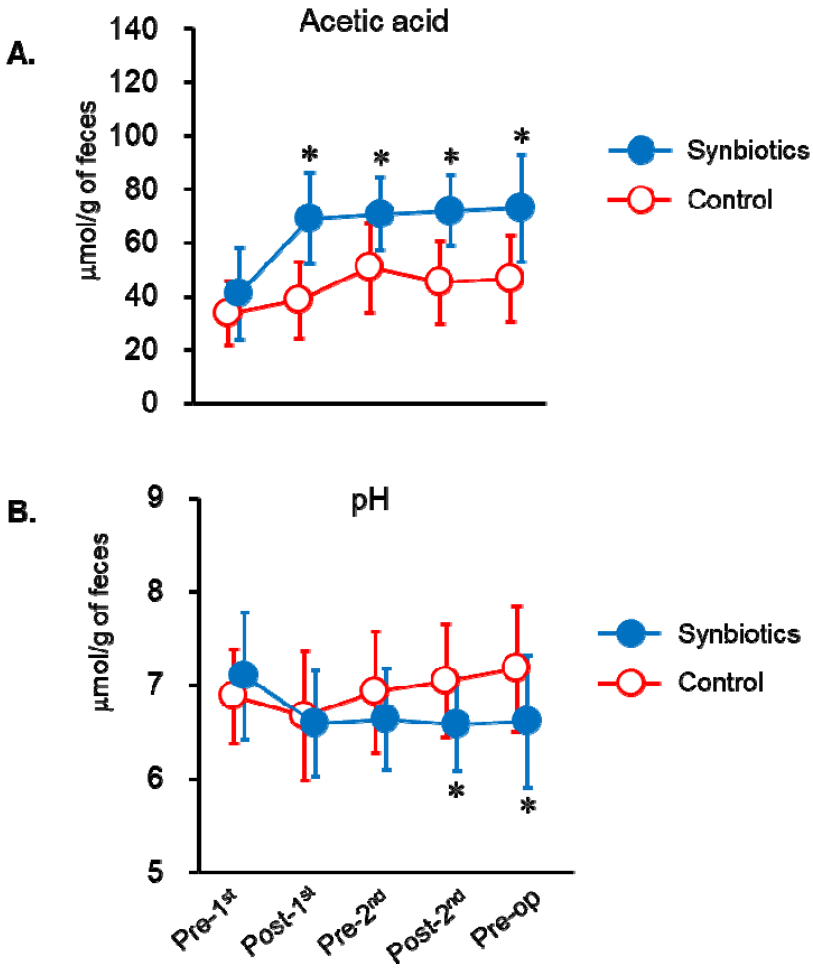

Figure 4.
Effect of synbiotics treatment on fecal organic acid concentrations and pH.
*p < 0.05 vs. control group.

Research Summary and Future Perspective

This study showed the beneficial effects of synbiotics treatment for preventing bacterial translocation during neoadjuvant chemotherapy and subsequent esophagectomy in patients with esophageal cancer. The incidence of gastrointestinal toxicity during chemotherapy was lower in the synbiotics group compared to the control group. Long-term administration of

synbiotics may lead to a favorable intestinal microenvironment and allow patients to tolerate neoadjuvant chemotherapy and subsequent highly invasive surgery. It is necessary to further investigate the mechanism that is related to the prevention of bacterial translocation by synbiotics.

Publication

Journal : Clinical Nutrition
Title : Impact of synbiotics treatment on bacteremia induced during neoadjuvant chemotherapy for esophageal cancer
Authors : Masahide Fukaya[a], Yukihiro Yokoyama[a], Hiroaki Usu[a], Hironori Fujieda[a], Yayoi Sakatoku[a], Takamasa Takahashi[a], Kazushi Miyata[a], Mai Niikura[c], Takuya Sugimoto[c] Takashi Asahara[c], Masato Nagino[d]
DOI : https://doi.org/10.1016/j.clnu.2021.10.004

Japanese ver. https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Cli_Nut_20211012.pdf