ORIGINAL ARTICLE

Effect of probiotic supplementation on bacterial translocation in common bile duct obstruction

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Abstract

Objective   To investigate the effects of probiotics on bacterial translocation in the obstructive common bile duct with comparison to an enteral product containing arginine and glutamine.

Material and method   In our study, 40 Sprague–Dawley rats each weighing 250–300 g were used. Animals in Group 1 (sham) were laparatomized and fed standard chow supplemented with physiologic saline at daily doses of 2 ml through orogastric tube for 7 days. Common bile ducts of the animals in the other groups were ligated with 3/0 silk sutures. Group 2 (control group) was fed standard chow supplemented with daily doses of 2 ml physiologic saline. Group 3 (probiotic group) was fed standard chow supplemented with a probiotic solution (Acidophilus plus) containing strains of *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Lactobacillus bulgaricus* at a daily doses of 2×10^9 colony forming units (CFU). Group 4 (formula group) was fed only an enteral solution (Stresson Multi Fiber) containing glutamine, arginine and a medium-chain fatty acid at daily doses of 2 g/kg. At the end of the 7th day, all animals were relaparatomized, and to determine bacterial translocation, aerobic, and anaerobic cultures were obtained from the specimens of mesenteric lymph nodes, intestinal mucosa, and blood samples. Smear cultures prepared from caecum were examined to determine the number of CFU. Finally, for histological examination specimens were excised from terminal ileum, and oxidative damage was assessed in liver tissues. Afterwards all animals were killed.

Results   Moderately lesser degrees of bacterial translocation, and mucosal damage were seen in Groups 3, and 4 relative to Group 2 ($p < 0.05$). In Group 4, any difference was not seen in the number of cecal bacteria relative to baseline values, while in Group 3, significant decrease in cecal colonization was seen. Among all groups, a significant difference between levels of malondialdehyde, and glutathione was not observed.

Conclusion   At the end of our study, we have concluded that both probiotics, and enteral diets which contain immunomodulators such as glutamine, and arginine alleviate bacterial translocation, and impairment of intestinal mucosa.

Keywords   Bacterial translocation · Common bile duct obstruction · Probiotics · Enteral feeding

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Introduction

Bacterial translocation is the passage of bacteria through mucosal barrier, and then from gastrointestinal system into

mesenteric lymph nodes, liver, spleen, etc. This passage does not occur under normal conditions. Disruption of integrity, and barrier function of intestinal mucosa, in cases of burn injuries, starvation, trauma, surgery, intestinal, and biliary tract occlusion, increases absorption and extrusion of bacteria with their resultant translocation into other organs [1–7].

Obstruction of the biliary flow into the duodenum, and accumulation of bile salts in the liver cells, and biliary tract is known as cholestasis. As a result of cholestasis, some pathological changes occur in the organism. Some of the predominant ones include reticuloendothelial system dysfunction, suppression of the immune system, structural, and functional changes in the intestinal mucosa, oxidative damage of the intestinal wall, blockade of the antibacterial, and detergent effects of bile salts secondary to their impaired enterohepatic circulation, bacteremia, and endotoxemia [1, 8–11].

Clinical and experimental studies have been, and will be conducted to disclose, and prevent the emergence of the mechanisms involving in bacterial translocation. Probiotics are non-pathogenic microorganisms which maintain, and promote microbial balance with ensuing enrichment of the flora. It has been reported that via their host protective impact on antimicrobial activity, resistance to bacterial colonization, stimulation of the immune system, and enzymatic activity, probiotic bacteria exert favorable effects on mucosal lining of oral cavity, gastrointestinal, upper respiratory tract, and urogenital system, and eventually flourish well-being, and decrease the risk of contracting a disease. Especially their effects on intestinal mucosa and immunity indicate the protective role of probiotics in conditions which might induce bacterial translocation [12–17].

Use of enteral products (also termed as immunomodulators) containing glutamine, arginine, nucleotides, and short-chain fatty acids which protect, and support immune functions of the intestine, decreases the rate of bacterial translocation [2, 18–22].

In the present study, we aimed to investigate the effects of probiotics on bacterial translocation, alterations in intestinal mucosa, and formation of free radicals induced by choledocal obstruction in comparison with those of an enteral product containing glutamine, and arginine.

Materials and methods

Our experimental study was performed in Istanbul University, Institute of Experimental Medicine, Research, and Application Center (DETAE). In this study, 40 Sprague–Dawley rats each weighing 250–300 g were used. All of the experimental animals were kept in metal cages without restricting their movements, and fed with water, and standard pellets under constant ambient conditions.

Under ketamine (100 mg/kg) plus xylazine (15 mg/kg) anesthesia, incision site was disinfected with povidone–iodine, and through a midline incision, the abdominal cavity was entered.

Group 1 (Sham group): After exposure of the common bile duct during laparotomy, the rats fed standard chow and received physiologic saline through an orogastric tube for 7 days at daily doses of 2 ml.

Common bile ducts of the animals in the other groups were ligated with 3/0 silk sutures.

Group 2 (control group) was fed standard chow supplemented with physiologic saline through an orogastric tube for 7 days at daily doses of 2 ml.

Group 3 (probiotic group) was fed standard chow supplemented with a probiotic mixture (Acidophilus plus, Pharmadass, Harrow, UK) containing strains of *Lactobacillus acidophilus* (2×10^9 CFU/capsule), *Bifidobacterium bifidum* (1×10^9 CFU/capsule) and *Lactobacillus bulgaricus* (1×10^9 CFU/capsule) at a daily doses of 2×10^9 CFU via an orogastric tube [23–25].

Group 4 (formula group) was fed with only an enteral solution (Stresson Multi Fiber, Nutricia, Istanbul, Turkey) containing 1,344 mg glutamine, 889 mg arginine, 1.5 g medium-chain fatty acid in each 100 ml of the diet solution at daily doses of 2 g/kg.

At the end of the 7th day, all rats were relaparatomized under ketamine plus xylazine anesthesia. In all animals, aerobic, and anaerobic cultures were performed in specimens of mesenteric lymph nodes (MLNs), and intestinal (terminal ileal) mucosa, and blood samples to determine bacterial translocation (BT). Smear cultures prepared from caecum were examined to determine the number of CFU. Finally, for histological examination specimens were excised from terminal ileum, and also oxidative damage was assessed to measure malondialdehyde (MDA) and glutathione (GSH) levels in liver tissue samples. Afterwards all animals were killed.

Microbiological analysis

Cecal samples were inoculated on Carry-Blair transport culture media, while specimens of mesentery, and ileum were placed in sterile Petri dishes. Blood samples were inoculated on the blood culture media. Samples other than blood were inoculated on agar culture media mixed with sheep blood for aerobic, and on Schaedler media for anaerobic bacteria. As a liquid culture media, a Schaedler bouillon made oxygen-free by boiling for 10 min was used. Burri–Wright method was employed to provide anaerobic conditions in this liquid media. All culture media were incubated at 35–37 °C for at least 24–48 h. For anaerobic cultures,

inoculated culture media were placed in GASPAK jars to provide anaerobic conditions. Petri dishes were examined 24 h later for the growth of aerobic microorganisms. Colonies in Petri dishes with bacterial growth were firstly stained with Gram dyes, and then bacterial identification was performed using routine classical methods. Presence of catalase-negative Gram-positive cocci, and DNAases, effect of Gram-negative cocci on various carbohydrates, and various enzymes were investigated. Forty-eight hours after incubation anaerobic growth on Petri dishes, and liquid medium were evaluated. From turbid liquid culture media priorly inoculations onto aerobic (blood agar), and anaerobic (Schaedler agar) media were performed, and then Petri dishes were incubated under suitable conditions.

For the identification of the species of anaerobic bacteria, in consideration of their Gram staining characteristics, antibiotic discs were used; then, they were inoculated on bile agar. Blood samples were inoculated on media used for hemoculture. From bottles demonstrating bacterial growth, inoculations were made on aerobic and anaerobic media for the identification of isolates.

Biochemical analysis

Determination of lipid peroxide and glutathione (GSH) levels in liver tissue

The livers of the animals were rapidly removed, washed in 0.9 % NaCl solution, and kept in ice. Liver tissue was homogenized in ice-cold 0.15 M KCl (10 %; w/v) solution. To assess lipid peroxidation, MDA levels were determined using thiobarbituric acid according to the method of Ohkawa et al. [26]. The breakdown (degradation) product of 1,1,3,3-tetraethoxypropane was used as a standard, and the results were expressed as nmol MDA/g tissue. GSH levels were measured in the homogenates by the method of Beutler et al. [27]. The method is based upon the development of a relatively stable yellow color when 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) is added to sulfhydryl compounds. After precipitation with metaphosphoric acid, supernatants were reacted with DTNB. Absorbance was read spectrophotometrically at 412 nm [27, 28].

Histopathological analysis

Small bowel specimens were fixed in buffered 10 % formaldehyde. After routine tissue treatments, 5–7 micron sections cut from the prepared paraffin blocks were stained with hematoxylin–eosin (HE), and periodic acid schiff (PAS) dyes, examined, and evaluated under light microscope. Pathological changes in the terminal ileum were interpreted according to Chiu classification [29]:
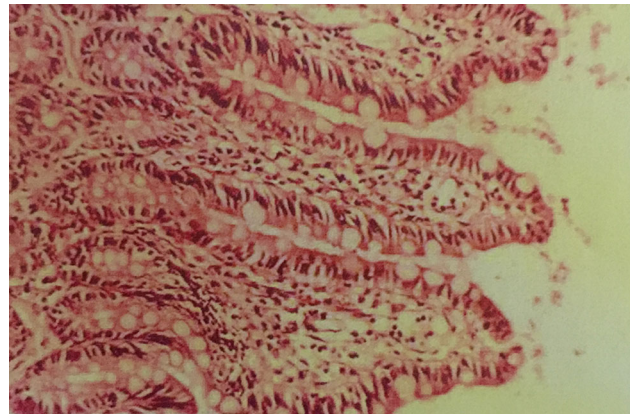

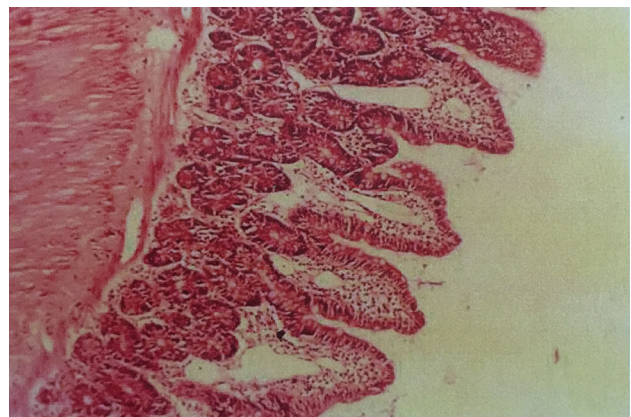**Fig. 1** Stage 0: normal appearance of the villus epithelium

Fig. 2 Stage 1: minimal detachment of the villus epithelium
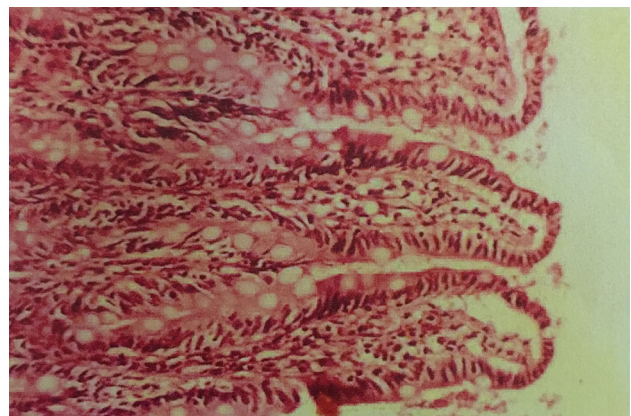

Fig. 3 Stage 2: moderate detachment of the villus epithelium and minimal edema in the lamina propria

Stage 0: normal mucosa (Fig. 1); Stage 1: subepithelial space, and capillary congestion (Fig. 2); Stage 2: subepithelial space was enlarged leading to moderate detachment of epithelial layer from lamina propria (Fig. 3); Stage 3: extensive detachment of epithelial layer from
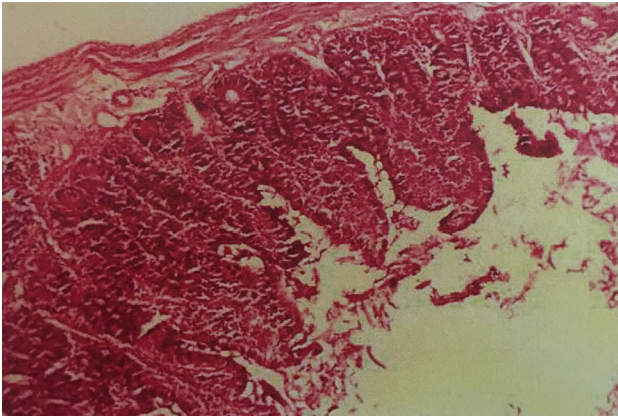
Fig. 4 Stage 3: marked detachment of the villus epithelium, lymphocyte, and plasmocyte infiltration in lamina propria
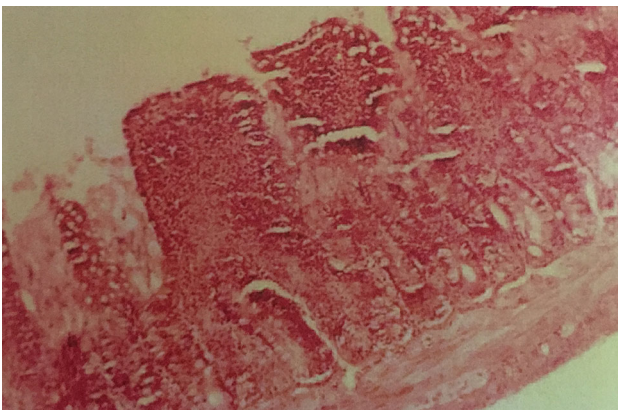

Fig. 5 Stage 4: desquamation of the villus epithelium

lamina propria (Fig. 4); Stage 4: loss of villi, capillary dilatation, hypercellularity in lamina propria (Fig. 5); Stage 5: areas of ulceration, bleeding, and destruction on lamina propria.

Statistical evaluation

For the assessment of bacterial translocation Fisher's Chi-square, Mann–Whitney U tests, and for the estimation of histological scores Mann–Whitney U test were used. For the evaluation of biochemical test results, one-way ANOVA test, and for multiple comparisons Tukey HSD test were preferred.

Results

Ten rats in each group amounting to a total of 40 animals were used in the study. During the study period none of the animals died.

Table 1 Rates of bacterial translocation into blood, and MLN

Groups	Blood	MLN
Group 1 ($n = 10$)	1 (10 %)	0 (0)
Group 2 ($n = 10$)	10 (100 %)	7 (70 %)
Group 3 ($n = 10$)	2 (20 %)	3 (30 %)
Group 4 ($n = 10$)	2 (20 %)	2 (20 %)

Table 2 Mean number of colonies in the cecal specimens

Group 1	100×10^3	*Escherichia coli*
Group 2	91.5×10^3	*E. coli*, *Proteus mirabilis*
Group 3	29.3×10^3	*E. coli*, *P. mirabilis*, *Klebsiella pneumoniae*
Group 4	109×10^3	*E. coli*, *P. mirabilis*, *K. pneumoniae*

Rates of bacterial translocation into blood, and MLNs categorized in groups are shown in Table 1. Rates of BT in Groups 3 and 4 were significantly lower relative to Group 2 ($p < 0.05$).

Mean number of colonies in the cecal specimens are shown in Table 2. Mostly *E. coli* was exposed to translocation. Significantly lesser number of cecal intraluminal bacteria was found in Group 3. Comparison of the number of colonies in the cecum differed significantly between the probiotic, control and formula groups ($p < 0.05$).

Distribution of histopathologic stages among groups is shown in Table 3. Any statistically significant difference between Groups 3, and 4 was not ($p = 0.34$) observed, while when results in both groups were compared with those of the Group 2 (control group), mucosal damage was seen less frequently in the Group 3 and 4 ($p < 0.05$) (Fig. 6).

When measurements of GSH, and MDA to determine oxidative damage in the liver tissue were compared, a statistically significant difference was not observed between groups (Table 4).

Discussion

Burn injury, starvation, surgical trauma, intestinal obstruction, shock, antibiotherapy result in intestinal mucosal damage, suppression of the immune system, altered balance among intestinal flora, and translocation of bacteria into tissues outside the gastrointestinal system [3, 4, 7, 30–35].

The mechanism of the bacterial translocation is not fully known. Disequilibrium between intestinal microflora, and host defense mechanisms (mucosal barrier, immunological defense, gastric acidity, and gastrointestinal motility) is thought to have a major role in bacterial translocation [36].

Table 3 Histopathological stages

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Group 1		2	4	4	
Group 2			3	5	2
Group 3	2	3	3	1	1
Group 4		3	4	3	

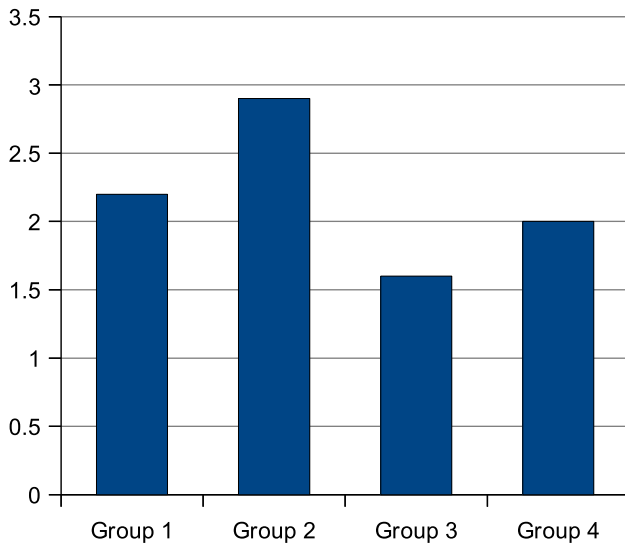

Fig. 6 Histopathological scores of the terminal ileum specimens

Table 4 Measurement of GSH and MDA levels

	Group 1	Group 2	Group 3	Group 4
GSH (μmol/g)	8.13 ± 1.59	8.49 ± 1.77	9.41 ± 1.45	8.77 ± 2.46
MDA (nmol MDA/g)	151 ± 52	175 ± 45	173 ± 53	221 ± 42

Cholestasis which occurs as a consequence of common bile duct obstruction leads to suppression of immune system, reticuloendothelial system dysfunction, oxidative damage of the intestinal wall, structural, and functional impairment of the guts resulting in bacterial translocation out of bowels [8, 9, 11].

Increased frequencies of bacterial translocation in obstructive jaundice have been clearly demonstrated in animal studies. Attenuation of immune functions and inflammatory response is the main etiological factor in the development of infectious complications in cases with obstructive jaundice [36].

In a study performed by Parks et al. [11], development of morphological alterations in mucosal layers of the terminal ileum, and increased rate of bacterial translocation were demonstrated in the bacterial cultures of blood samples, and specimens of MLN, liver, and spleen harvested 1 week after induction of obstructive cholestasis when compared with the control group.

In our study, we have also observed increased bacterial growth in blood, and MLN cultures of the animals with ligated common bile ducts relative to only laparatomized group. Rates of bacterial translocation into blood and MLN were found to be 100 and 70 %, respectively.

In animal models of experimentally induced cirrhosis, antibiotherapy administered to prevent bacterial infections, and to suppress aerobic intestinal flora was found to be effective. However, especially in patients under long-term prophylaxis, gradually increasing resistance against antibiotics was observed. For this reason, probiotics which contain live microorganisms have been introduced into clinical practice. These probiotics are included in the category of functional nutrients, and defined as physiologically active ingredients which apart from their main nutritional characteristics, they stabilize the balance between intestinal flora, and exert beneficial effects on the health state [25].

Probiotics are microorganisms which flourish the characteristics of the endogenous microflora so as to demonstrate favorable effects on the health state of the host. It has been reported that probiotics exert indirect and direct effects on intestinal physiology, stimulate immune system, influence gastrointestinal system, upper respiratory tract, and urogenital system mucosa, improve health state, and have a potential to decrease risk of contracting disease. Probiotic bacteria demonstrate antagonistic and resistive effects against bacterial colonization, and also have immunologic, antimutagenic, and antigenotoxic effects which all influence intestinal microflora favorably [13, 14, 36].

Chiva et al. [25] investigated the effects of *Lactobacillus johnsonii La1* strains and antioxidants on patients with experimentally induced cirrhosis, and demonstrated decreased rates of bacterial translocation and endotoxemia in the group of animals fed with probiotics alone or in combination with an antioxidant.

Bauer et al. [24] disclosed relatively lower bacterial translocation rates in the group of rats with CCL4-induced cirrhosis fed with a strain of *Lactobacillus*.

We also observed extremely decreased bacterial translocation in blood samples, and mesenteric lymph node specimens, and markedly lower number of bacterial colonies in the caecum of the rats fed with a probiotic solution (Acidophilus Plus) containing strains of *L. acidophilus*, *B. bifidum* and *L. bulgaricus*. Besides, histopathologic examination revealed reduced levels of mucosal damage when compared with the control group.

Intestines require glutamine, arginine, nucleotides, and medium-chain fatty acids for the maintenance of their normal immune functions. Therefore, many enteral solutions are prepared so as to contain these ingredients. Use of these immunomodulator diets decrease rates of bacterial translocation [29, 37]. Glutamine is a more important source of energy for enterocytes, and colonocytes than glucose. In animal experiments, glutamine has been shown to enhance intestinal mucosal functions, repair, and development. Conditions like sepsis, trauma, surgery, and shock induce decreases in blood glutamine levels. Clinical studies have demonstrated ameliorating effects of glutamine supplementation on clinical outcomes in catabolic patients [18, 20, 38–40].

Erbil et al. investigated the effects of deoxycholate, lactulose, and glutamine on induced bacterial transloca-tion in cases with obstructive common bile duct. All of three products demonstratedly decreased bacterial trans-location, being most prominent in the glutamine group. The authors also revealed decreased malondialdehyde, and myeloperoxidase activity in the glutamine group [41].

In a study performed by Schimple et al. [42], rats with experimentally induced obstructive jaundice, and chronic portal hypertension were fed with glutamine, allopurinol, glutamine + allopurinol, and decreased rates of bacterial translocation, and malondialdehyde, and myeloperoxidase activity were demonstrated in the allopurinol and gluta-mine groups.

We also observed significantly lower bacterial translo-cation rates in blood, and MLN samples, and also decreased intestinal mucosal damage in Group 4 fed with Stresson Multi Fiber diet which contains glutamine, argi-nine, and medium-chain fatty acids. Cecal bacterial growth was not different from that of the control group. However, favorable changes were not seen in the levels of MDA, and GSH.

In comparisons between the probiotic, and the formula groups, a statistically significant difference was not observed as for their ameliorating effects on rates of bac-terial translocation, and intestinal mucosal injury. Though probiotics significantly decreased the number of bacterial colonies in the cecum, any relevant effects of enteral pro-ducts containing glutamine, and arginine were not seen. In our study, in all groups, any significant difference was not observed between hepatic levels of MDA, and GSH which are indicators of oxidative damage.

At the end of our study, we have concluded that both probiotics, and immuno-modulating diets prevent bacterial translocation, and intestinal damage occurring following obstructive cholestasis, and they can be used in the treat-ment of conditions which might induce bacterial translocation.

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