Probiotics and Antimicrobial Proteins
https://doi.org/10.1007/s12602-021-09764-w

The Roles of *Lactobacillus Acidophilus* and Pectin in Preventing Postoperative Sepsis and Intestinal Adaptation in a Rat Model of Short Bowel Syndrome

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Accepted: 25 February 2021

Abstract
One of the primary causes of morbidity and mortality in those with short bowel syndrome (SBS) is sepsis, caused by bacterial translocation (BT). Since synbiotics can cease gut-related bacterial overgrowth, they may serve as a supportive dietary supplement–based strategy after gastrointestinal surgery. This study was conducted to determine the effects of *Lactobacillus acidophilus* and pectin on BT and gut adaptation after extensive small bowel resection in the rat. Forty rats were distributed in four groups. Group A suffered laparotomy, group B suffered gut transection and reanastomosis, SBS rats (group C) suffered 75% small gut resection, and finally, Group D suffered gut resection and treated with a synbiotic cocktail from day 7 before the surgery to day 14 after it. Intestinal structural changes and BT to mesenteric lymph nodes, liver, portal blood, and peripheral blood were detected on day 15 post-surgery. Treatment with a synbiotic cocktail led to a considerable reduction in bacterial translocation to liver and portal vein (degree II) compared with SBS untreated rats. Also, synbiotic administration significantly increased jejunum and ileum villus height and crypt depth, ileum villus width, and percentage of goblet cells in jejunum and ileum compared with SBS rats. In the rat model of short bowel syndrome, *L. acidophilus*, and pectin, as a potential synbiotic compound, could decrease the BT from the gut and improve the bowel adaptation.

Keywords Short bowel syndrome · *Lactobacillus acidophilu* · Pectin · Bacterial translocation · Intestinal adaptation

Introduction

Intestinal failure (IF) has been described as a significant decrease of well-functioning bowel mass under the minimum amount essential for sufficient digestion and absorption to provide nutrients and fluid for maintenance and growth in humans and animals[1]. Short bowel syndrome (SBS) is amongst the principal reasons for gut failure. It can result from congenital disease of enterocytes, surgical resection of diseased gut segments, gastroschisis, omphalocele, intestinal atresia, midgut volvulus, Hirschsprung's disease, or abnormalities of the superior mesenteric artery [2]. The outcomes of massive small bowel resection are dilated dysmotility, bacterial overgrowth, reduced gut barrier function, impaired intestinal transit time, and decreased local immune system to gut microorganisms [3]. According to the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), probiotics are live organisms with beneficial effects on the host when being administered in sufficient amounts [4, 5]. These microorganisms are being used as a cure for some medical conditions like gastrointestinal (GI) disorders [1]. It has been proven that probiotics are effective in maintaining the intestine microbiota ecosystem in humans and animals [6]. Prebiotics are non-digestible food component fibers that positively affect the host by selectively inducing the growth and activity of probiotic bacteria like lactobacilli and bifidobacteria [7]. Potentially associated with health, synbiotics are the mixtures of probiotics and prebiotics and are believed to be more beneficial in terms of gut health and function [8]. *Lactobacillus*, an inhabitant of the natural gastrointestinal environment, excretes bacteriocins, acetic and lactic acid. It

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Published online: 14 March 2021

prohibits the growth and attack of pathogenic microorganisms and reduces the creation of pro-inflammatory cytokines including IFNγ, tumor necrosis factor α, and IL12. Also, it stimulates the production of IgA, raises mucin production, and prevents pathogenic bacterial colonization [9].

Strains of lactic acid bacteria (LAB) belonging to the genera *Lactobacillus* are commonly used as probiotics. Probiotic formulations often contain strains of *Lactobacillus salivarius*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactococcus lactis*, *Lactobacillus plantarum*, and *Lactobacillus rhamnosus* [10].

L. acidophilus has been used in different studies as a probiotic in gastrointestinal surgeries. For example, Diepenhorst et al. (2011) have used a multispecies probiotic mixture (Ecologic 641) containing *L. acidophilus* in pancreatoduodenectomy [11]. Anderson et al. (2004) have used a synbiotic therapy consisting of *Lactobacillus acidophilus* La5, *Lactobacillus bulgaricus*, *Bifidobacterium lactis* Bb-12, and *Streptococcus thermophilus* in surgery [12]. Also, Zhang et al. (2013) have used a synbiotic composition containing *Lactobacillus acidophilus* in preventing post-surgery infection in liver transplant cases [13]. Finally, in the study by Gaon, both *Lactobacillus casei* and *L. acidophilus* strains cerela were efficient in curing chronic diarrhea caused by bacterial overgrowth [14]. *Lactobacillus acidophilus* strain ATCC 4356 is cited in different articles as an organism that confers probiotic effects when being incorporated into fermented food products [15]. It was initially isolated from human infant feces in 1900. This strain is a significant inhabitant of the gastrointestinal tract with reported probiotic properties [16]. Campana et al. (2012) have investigated the potential probiotic activity of *Lactobacillus acidophilus* ATCC 4356 against several human *Campylobacter jejuni* isolates, which caused a significant reduction of adhesion/invasion of pathogens to intestinal cells [17]. Also, Bassyouni et al. (2015) have studied the antimicrobial potential of *Lactobacillus acidophilus* ATCC 4356 on pathogenic bacteria causing diarrhea. It could decrease the colony count of tested strains and improve the antibacterial effect of tested antibiotics against ETEC, *S. typhimurium* and *S. aureus*, and *S. flexeneri* [18]. In 2019, Rezaee et al. have evaluated the antibacterial activity of lactobacilli probiotics (*Lactobacillus acidophilus* ATCC 4356, *Lactobacillus rhamnosus* ATCC 7469, *Lactobacillus reuteri* ATCC 23272, *Lactobacillus fermentum* ATCC 9338, *Lactobacillus plantarum* ATCC 8014, and *Lactobacillus casei* ATCC 39392) on clinical strains of *Helicobacter pylori*. These strains could decrease the count of *H. pylori*, inhibit its urease activity, and reduce its adhesion to epithelial cell lines. This may be significant for the impact of *H. pylori* colonization in the host stomach [19]. Pectin as a soluble fiber is more completed fermented and has a higher viscosity than insoluble fibers. It has been used in synbiotics that contained different lactic acid bacteria in patients undergoing pancreatic resections [20], liver transplantation [21], and pancreatoduodenectomy [22]. So, we hypothesize that *L. acidophilus* and pectin will act as a potential synbiotic compound on BT in a rat short bowel model.

Materials and Methods

Animals

This pilot study was conducted following the guidelines for the care and application of laboratory animals, University of Tabriz, Iran. Forty-six weeks Wistar male rats weighing 200–250 g were placed in individual cages. They were acclimatized for a week before the procedure with free access to water and being fed by a standard rat chow [3].

Test Microorganisms

The commercial lyophilized culture of the *Lactobacillus acidophilus* ATCC 4356 was purchased from the Iranian Organization of Industrial Research. The subcultivation and preparation of this probiotic strain were carried out under the standard method. The pour plate procedure was used for the enumeration of *Lactobacillus* cells in a synbiotic solution. MRS agar (Merck, Darmstadt, Germany) was applied to *L. acidophilus* enumeration [23].

Experimental Design

Rats were scattered into four groups of 10 animals each. Group A rats suffered laparotomy, group B suffered gut transection and reanastomosis, group C suffered 75% intestine resection (SBS), and finally, group D suffered gut resection and was cured using *L. acidophilus* strain ATCC 4356 (1×10^{10} CFU per rat per day) and pectin at a dose of 2.5 g per animal per day in drinking water. The animals in group D were treated with the synbiotic composition containing *L. acidophilus* and pectin from day 7 before the surgical procedure to day 14 after it. The amount of ingested synbiotic was adjusted for each rat based on water intake. The solution was prepared each day following the amount of consumed water during the last day [11, 21, 24]. The pectin addition was compensated in the A, B, and C groups with the same saline solution volume.

Surgical Procedure

After overnight fasting, rats were anesthetized with intra peritoneal ketamine (90 mg/kg) and xylazine (10 mg/kg). Applying sterile methods, a midline laparotomy was conducted. Group B rats suffered the transection of the ileum

15 cm proximal to the ileocecal junction and reanastomosis. SBS animals suffered 75% small gut resection, remaining 5 cm of proximal jejunum and 10 cm of the distal ileum. All anastomoses were carried out using interrupted sutures of 6–0 Dexon. Before abdominal closure, all of the rats were intraperitoneally treated with 3 ml warm 0.9% saline. All rats were kept in individual cages, permitted to consume water ad libitum on the first postoperative day and standard chow on the second day, and observed over 14 days (Fig. 1) [3].

Bacterial Translocation

On the morning of the 15th day, all animals were anesthetized using a subcutaneous cocktail of ketamine and xylazine. Both the chest and abdomen were shaved, and then midline laparotomy and thoracotomy were conducted. Samples were collected to determine the colony-forming unit (CFU) index and bacterial species by Gram staining, and common biochemical reactions. Blood samples (1 ml) were collected from the portal vein (portal blood) and the left ventricle (peripheral blood) and cultivated into aerobic brain heart infusion broth media and incubated for 7 days. Then, passages were performed on blood agar, eosin-methylene blue (EMB), MacConkey, and Mannitol salt agar mediums (Sigma Aldrich, Saint Louis, Missouri, USA). One-gram samples were collected from the mesenteric lymph nodes and liver left lobe, homogenized in 1 ml of sterile salt solution, and placed onto sterile blood agar, EMB, MacConkey, and Mannitol salt agar. All plates were then incubated for 25 to 48 h under aerobic conditions at 37 °C. Bacterial detection was conducted using conventional assays like catalase, oxidase, and coagulase for Gram-positive and identification gallery for *Enterobacteria* in Gram-negative. Bacterial translocation of lactobacilli was determined from the bacterial cultures of intestine origin applying special agars. Bacterial translocation was diagnosed positive when a bacterial culture of enteric origin was identified in at least one sample [24]. BT was classified into three degrees: local or degree I (mesenteric lymph nodes), regional or degree II (portal blood and, or liver), and systemic or degree III (peripheral blood) [25].

Histopathological Examination

Tissue specimens belonging to the proximal jejunum and distal ileum were harvested from five rats in each group and fixed in 10% formalin solution and then paraffin-embedded

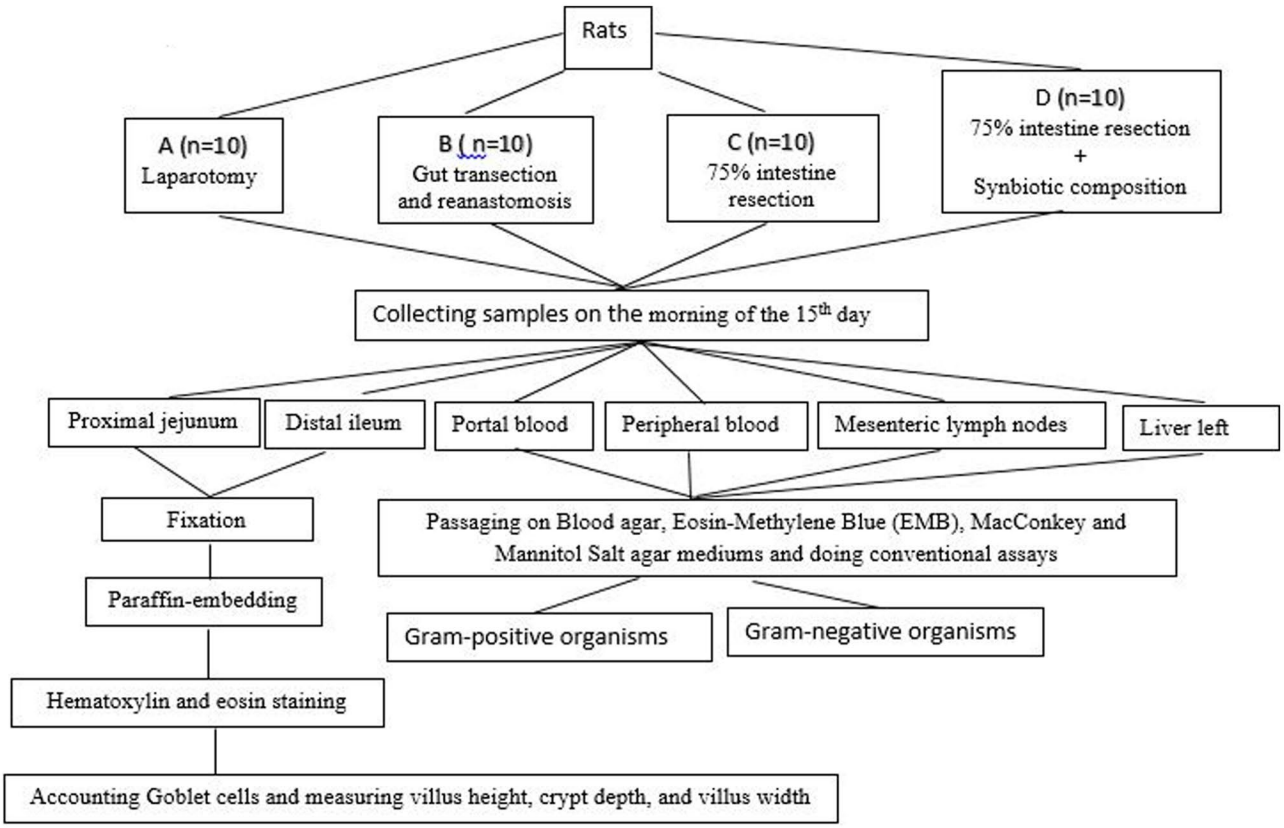

Fig.1 Flowchart of the experiment

Table 1 Frequency of bacterial translocation to blood and peripheral organs (% of rats exhibiting bacterial translocation)

Groups	Mesenteric lymph nodes	Portal blood	Liver	Peripheral blood
A (laparotomy)	20%	20%	10%	0
B (laparotomy and bowel transection)	20%	10%	0	0
C (SBS)	100%[a,b]	80%	100%[a,b]	60%[a,b]
D (SBS and treatment with cocktail)	100%[a,b]	20% [c]	40%[b,c]	40%[b]

$p \leq 0.05$

[a]Significant difference with group A

[b]Significant difference with group B

[c]Significant difference with group C

applying standard methods. After preparing 5-μm sections, the slides were stained using hematoxylin and eosin for histopathological study. Goblet cells were accounted and villus height, crypt depth, and in each ilium and jejunum samples, villus widths were measured in micrometers using an ocular micrometer (×20) on ten good-orientated villi and crypts [3, 25].

Statistical Analysis

The data were mentioned as mean ± SEM. The paired student *t* test and the nonparametric Kruskal–Wallis analysis of variance tests were applied for statistical analysis, with $p < 0.05$ statistically considered significant.

Results

Bacterial translocation analysis

Group A animals expressed 20% BT to the mesenteric lymph nodes (degree I), 10 to 20% BT to portal blood and liver (degree II), and no BT to peripheral blood (degree III). Group B animals demonstrated identical BT to the mesenteric lymph nodes (degree I) and 0–10% BT to portal blood and liver and no BT to peripheral blood (degree III). Massive small bowel resection in group C led to 100% BT to lymph nodes (degree I), 80–100% BT to portal blood and liver (degree II), and 60% BT to peripheral blood (degree III). Treatment with *L. acidophilus* and pectin in group D led to 20–40% BT to the liver and portal vein (degree II) and 40% BT to peripheral blood (degree III). But this treatment did not significantly alter the BT rate to the mesenteric lymph nodes (degree I) compared with SBS rats (Table 1). The results of statistical analysis showed that there were no substantial differences between groups A and B in BT rates of all levels. Group C (SBS rats) demonstrated significant differences in BT rates to mesenteric lymph nodes, liver, and peripheral blood compared to group A. Also, there was only a significant difference between groups D and A in BT rates to the mesenteric lymph nodes. Group B exhibited substantial differences in BT rates to all levels with groups C and D. Finally, group C rats showed only substantial differences with group D in BT rates to the liver and portal blood (degree II), $p \leq 0.05$ (Table 1).

The results of the types of microorganisms present in blood and tissue samples are shown in Table 2. According to these results, *E. coli* and *Staphylococcus aureus* were the most common Gram-negative and Gram-positive microorganisms, respectively. There was not any lactobacilli growth in blood and tissue samples from different groups. No difference was determined in the CFU of bacteria present in blood and tissue samples between the groups ($p \leq 0.05$).

Histopathological Findings

The mean and standard error values of goblet cell enumeration, villus height and width, and crypt depth are shown in Table 3. The results of the histopathological evaluation

Table 2 Microorganisms identified in blood and tissue samples

Microorganisms	Group B ($n = 10$)	Group C ($n = 10$)	Group D ($n = 10$)
Gram-negative organisms			
Escherichia coli	2(20%)	4(40%)	2(20%)
Enterococcus faecalis	0	2(20%)	1(10%)
Proteus mirabilis	0	0	2(20%)
Gram-positive organisms *Staphylococcus aureus*	3(30%)	3(30%)	1(10%)

Table 3 Effect of bowel resection and treatment with *L. acidophilus* and pectin on intestinal parameters

Parameters	Group A ($n=10$)	Group B ($n=10$)	Group C ($n=10$)	Group D ($n=10$)
Villus height (μm)				
Jejunum	454 ± 17.7	493 ± 5.3	529 ± 11.4[a]	609 ± 24.9[a,b,c]
Ileum	280 ± 11.4	287 ± 12.4	282 ± 10.5	325 ± 8.0[a,c]
Crypt depth(μm)				
Jejunum	172 ± 7.5	180 ± 4.1	192 ± 3.3	234 ± 9.2[a,b,c]
Ileum	163 ± 3.7	162 ± 8.3	181 ± 3.3[a,b]	217 ± 5.8[a,b,c]
Villus width				
Jejunum	93 ± 5.8	102 ± 6.0	110 ± 7.0	127 ± 3.0[a,b]
Ileum	108 ± 6.6	106 ± 8.8	104 ± 9.2	138 ± 5.8[b,c]
Percentage of goblet cells				
Jejunum	21 ± 1.1	20 ± 68	24 ± 0.9	29 ± 1.3[a,b,c]
Ileum	28 ± 1.2	29 ± 1.3	32 ± 1.5	45 ± 1.2[a,b,c]

$p \leq 0.05$

[a]Significant difference with group A

[b]Significant difference with group B

[c]Significant difference with group C

of intestinal parameters revealed that there were not any actual changes between groups A and B in all the studied parameters. SBS rats exhibited a substantial rise in jejunum villus height and ileum crypt depth compared with group A and ileum crypt depth compared with group B ($p \leq 0.05$). Compared with group A, utilizing *L. acidophilus* and pectin in group D led to considerable growth in all studied parameters except for ileum villus depth. Also, parameters like jejunum villus height, jejunum and ileum crypt depth, jejunum and ileum villus width, and percentage of goblet cells in ileum and jejunum in group D were significantly higher than group B. Also, in this group, jejunum and ileum villus height and crypt depth, ileum villus width, and percentage of goblet cells in jejunum and ileum increased significantly compared with group C ($p \leq 0.05$) (Figs. 2, 3, 4, and 5).

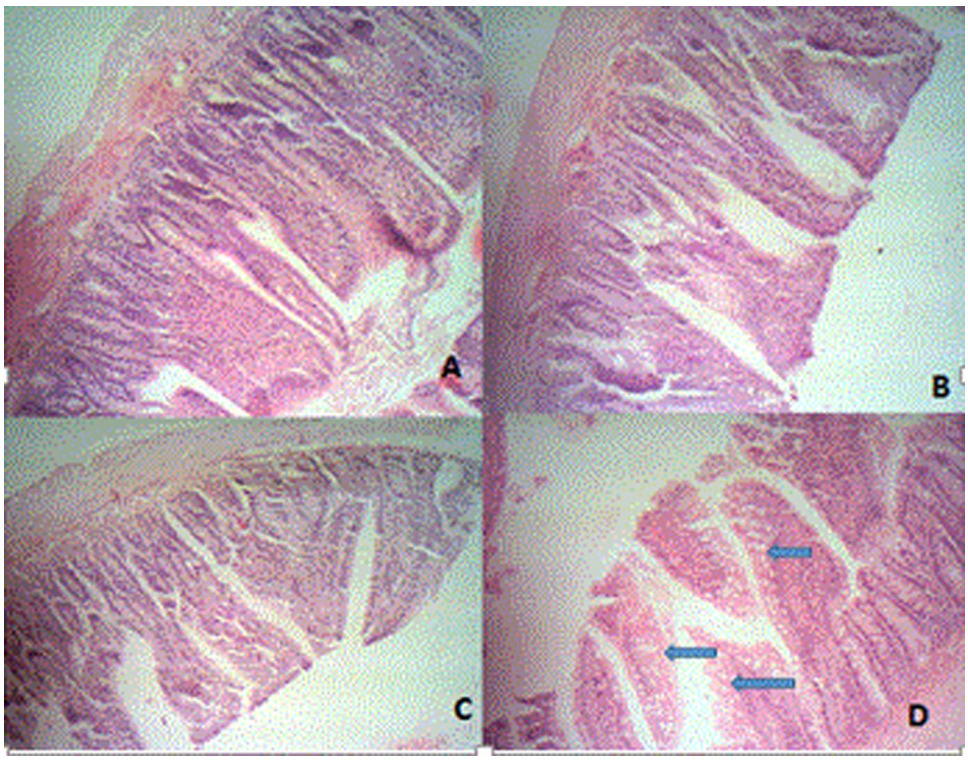

Fig. 2 After the usage of synbiotic compound, goblet percentage increased in jejunum, and this rise was statistically significant. **A** Jejunum of the group A with normal goblet percentage. **B** Jejunum of the group B with normal goblet percentage. **C** Jejunum of the group C with normal goblet percentage. **D** Jejunum with goblet hyperplasia in the group D (arrows). H&E staining. × 200

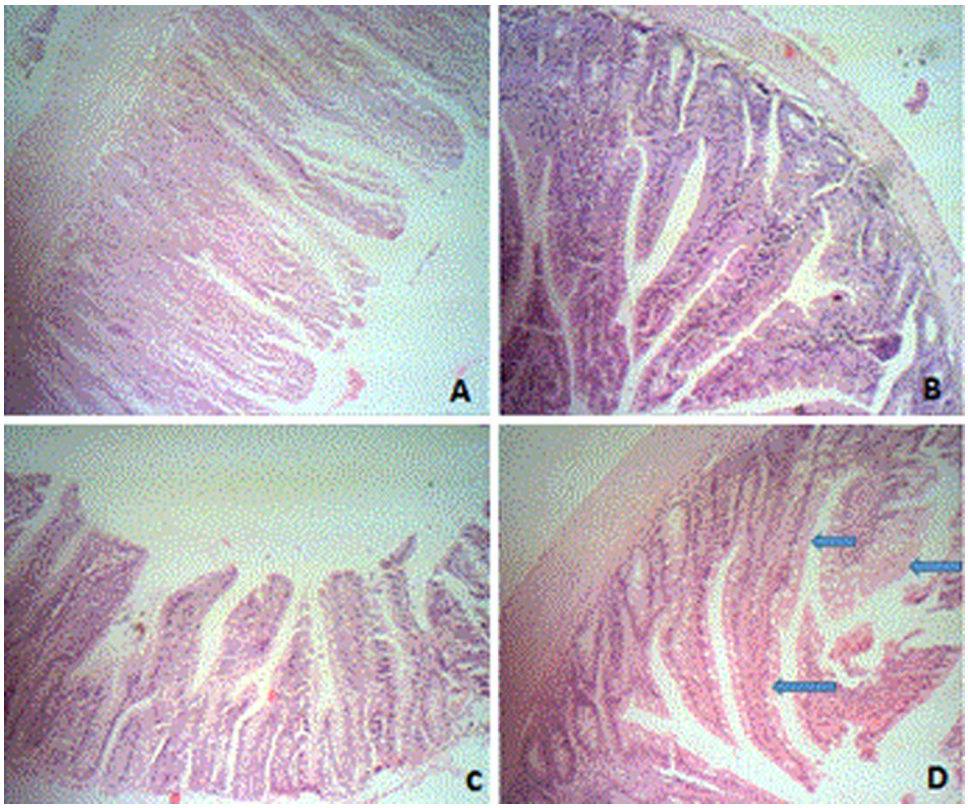

Fig. 3 After the usage of synbiotic compound, goblet percentage increased in ileum, and this rise was statistically significant **A** ileum of group A with normal goblet percentage. **B** Ileum of group B with normal goblet percentage: **C** Ileum of group C with normal goblet percentage. **D** Ileum with goblet hyperplasia in the group D (arrows). H&E staining. ×200

Discussion

Many patients with short bowel syndrome experience life-threatening infections. Gram-negative septicemia may be caused by the organisms of intestinal origin from bacterial translocation, which is influenced by dysmotility, microbial overgrowth, loss of intestine-associated lymphoid tissue, and mucosal atrophy [24]. The vast application of antimicrobials in patients undergoing GI surgery has led to the occurrence of multi-resistant bacteria. Some experimental works have demonstrated that probiotic bacteria may decrease the pathogenic microorganisms and restore an impaired barrier function. Therefore, it is essential to examine whether probiotics with such properties could be applied in presurgical preventions [26, 27]. Rayes et al. (2007) studied the effects of using synbiotics consisting of lactic acid bacteria and some prebiotics on patients undergoing pancreatoduodenectomy. There was a considerable decrease in post-surgery infections and even a limited hospital recovery in the synbiotic group [22]. In another study, the effects of a synbiotic formulation of *Lactobacillus casei*, *Bifidobacterium*, and galactooligosaccharides were evaluated in patients undergoing biliary surgery. When the synbiotic mixture was applied both before and after

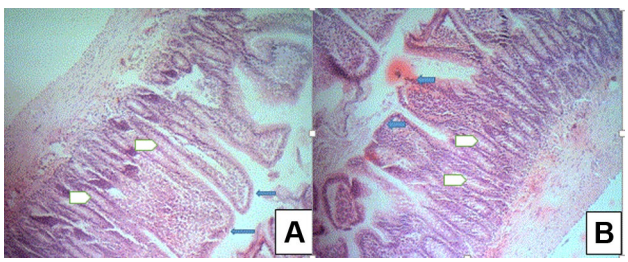

Fig. 4 Jejunum villus height (blue arrows) and crypt depth (white arrows) were increased significantly in the group D (photo microgram **B**) which suffered gut resection and cured using *L. acidophilus* and pectin compared with the group C (photo microgram **A**) which suffered 75% intestine resection. H&E staining. ×200

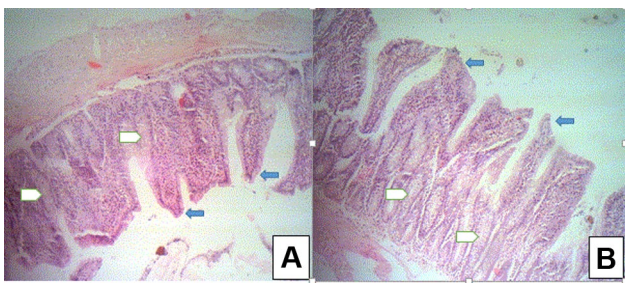

Fig. 5 Ileum villus height (blue arrows) and crypt depth (white arrows) were increased significantly in the group D (photo microgram **B**) which suffered gut resection and cured using *L. acidophilus* and pectin compared with group C (photo microgram **A**) which suffered 75% intestine resection. H&E staining. ×200

surgery, there was a substantial decline in post-procedure infection rate [28]. The impact of perioperative utilization of synbiotics containing *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus casei*, *Bifidobacterium*, and fructooligosaccharides on the appearance of surgical wound infection in patients suffered surgery for colorectal cancer was evaluated by Flesch et al. in 2017 [29]. The perioperative utilization of synbiotics considerably limited the postoperative infection rates in patients. Here, we studied the protective effects of *L. acidophilus* and pectin as a probable synbiotic compound on a rat model of SBS. Pectin can protect probiotic bacteria during the GI passage and identify the features related to its functionality [30]. We demonstrated that if the administration was started from 7 days before the intestinal surgery until 14 days after the procedure, it could reduce the BT rate of level II (liver and portal blood), which is similar to the results of Sugawaral et al. (2006) [28]. Also, Zhang et al. (2013) have used the synbiotic composition of probiotics like *L. acidophilus*, *L. plantarum*, *Biffidobacterium lactis*, *L. casei*, and *L. rhamnosus* and a low-fiber formula as prebiotic to prevent bacterial sepsis in patients undergoing liver transplantation. Combined prebiotics and probiotics could reduce the occurrence of bacterial infections and limit the duration of antibiotic therapy after liver transplantation. In this study, we also used a synbiotic cocktail of *L. acidophilus* and pectin in SBS rats. Our results were similar to Zhang et al. [13]. In 2008, Sukhotink et al. have studied the effects of lactulose on BT and gut adaptation in the rat model of SBS. Treatment with lactulose as a prebiotic did not change the bacterial translocation rates and the species of the most prevalent microorganisms. *E. coli* and *Klebsiella pneumoniae* were the most common bacteria detected. However, *Enterococcus faecalis* and *Enterobacter* species were less prevalent. Small bowel resection significantly increased the jejunal and ileal villus height and crypt depth compared with the rats undergoing bowel transection. Treatment with lactulose decreased villus height in jejunum and crypt depth in ileum compared with SBS animals [25]. In our study, using the synbiotic cocktail of *L. acidophilus* and pectin led to the significant decline of BT rate to liver and portal vein (degree II). It did not considerably alter the BT rate to mesenteric lymph nodes (degree I) and peripheral blood (degree III). Also, *E. coli* and *S. aureus* were the most common Gram-negative and Gram-positive organisms isolated in our study, respectively. Histological findings revealed that treatment with the above synbiotic compound significantly increased the jejunum and ileum villus height and crypt depth compared with bowel transection and SBS groups, which are not consistent with Sukhotnik et al. studies [25]. Also, in another study, the effects of *L. rhamnosus* GG on intestinal adaptation and BT after massive small bowel resection in rats were evaluated. SBS rats demonstrated a high percentage of BT (100%) to mesenteric lymph nodes and liver and 40% BT to peripheral blood. Administration of probiotics led to a significant decline in BT to all three organs. In our study, treatment with the synbiotic cocktail led to a considerable decrease in BT to liver and portal vein. While the BT rates to mesenteric lymph nodes and peripheral blood did not alter significantly. Also, according to Mogilner's study, SBS rats exhibited substantial growth in villus height and crypt depth compared with the sham group and SBS-probiotic rats revealed considerable amplification (Vs. SBS rats) in crypt depth in the ileum. These results are similar to our findings [3].

Conclusion

In conclusion, the synbiotic cocktail of *L. acidophilus* and pectin can ensure protection against BT in SBS and increase intestinal adaptive response.

Funding This work is supported by the University of Tabriz.

Data Availability Data will be available on reasonable request.

Declarations

Research Involving Human and Animal Participants The animal experiments were approved by a committee of the University of Tabriz (approval document No. 2558526, and the date when the study was approved: 23 August 2019).

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