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ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Dmitry Victorovich Garbuzenko, MD, PhD, DSc (Med), Professor, Department of Faculty Surgery, South Ural State Medical University, Chelyabinsk 454092, Russia. garb@inbox.ru

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Randomized Controlled Trial

Effect of probiotics on hemodynamic changes and complications associated with cirrhosis: A pilot randomized controlled trial

Roman Maslennikov, Irina Efremova, Vladimir Ivashkin, Maria Zharkova, Elena Poluektova, Elena Shirokova, Konstantin Ivashkin

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Roman Maslennikov, Irina Efremova, Vladimir Ivashkin, Maria Zharkova, Elena Poluektova, Elena Shirokova, Konstantin Ivashkin, Department of Internal Medicine, Gastroenterology and Hepatology, Sechenov University, Moscow 119435, Russia

Roman Maslennikov, Vladimir Ivashkin, Elena Poluektova, The Scientific Community for Human Microbiome Research, Moscow 119435, Russia

Roman Maslennikov, Consultative and Diagnostic Center No. 2 of Moscow Health Department, Moscow 107764, Russia

Corresponding author: Roman Maslennikov, MD, PhD, Assistant Professor, Department of Internal Medicine, Gastroenterology and Hepatology, Sechenov University, Pogodinskaya Street 1, Moscow 119435, Russia. mmmm00@yandex.ru

Abstract

BACKGROUND

Bacterial translocation exacerbates the hyperdynamic circulation observed in cirrhosis and contributes to a more severe disease course. Probiotics may reduce bacterial translocation and may therefore be useful to redress the circulatory imbalance.

AIM

To investigate the effect of probiotics on hemodynamic parameters, systemic inflammation, and complications of cirrhosis in this randomized placebo-controlled trial.

METHODS

This single-blind randomized placebo-controlled study included 40 patients with Child-Pugh class B and C cirrhosis; 24 patients received probiotics (*Saccharomyces boulardii*) for 3 mo, and 16 patients received a placebo over the same period. Liver function and the systemic hemodynamic status were evaluated pre- and post-intervention. Echocardiography and simultaneous blood pressure and heart rate monitoring were performed to evaluate systemic hemodynamic indicators. Cardiac output and systemic vascular resistance were calculated.

RESULTS

Following a 3-mo course of probiotics in comparison to the control group, we

observed amelioration of hyperdynamic circulation [a decrease in cardiac output ($P = 0.026$) and an increase in systemic vascular resistance ($P = 0.026$)] and systemic inflammation [a decrease in serum C-reactive protein levels ($P = 0.044$)], with improved liver function [an increase in serum albumin ($P = 0.001$) and a decrease in the value of Child-Pugh score ($P = 0.001$)] as well as a reduction in the severity of ascites ($P = 0.022$), hepatic encephalopathy ($P = 0.048$), and cholestasis [a decrease in serum alkaline phosphatase ($P = 0.016$) and serum gamma-glutamyl transpeptidase ($P = 0.039$) activity] and an increase in platelet counts ($P < 0.001$) and serum sodium level ($P = 0.048$).

CONCLUSION

Probiotic administration was associated with amelioration of hyperdynamic circulation and the associated complications of cirrhosis.

Key Words: Gut; Gut-liver axis; Microbiota; Hemodynamics; Heart; Gut-heart axis; *Saccharomyces boulardii*; Portal hypertension

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Core Tip: Bacterial translocation exacerbates the hyperdynamic circulation observed in cirrhosis and contributes to a more severe disease course. Probiotics may reduce bacterial translocation and may therefore be useful to redress the circulatory imbalance. The aim of the study was to investigate the effect of probiotics on hemodynamic parameters, systemic inflammation, and complications of cirrhosis in this randomized placebo-controlled trial. Following a 3-mo course of probiotics, we observed amelioration of hyperdynamic circulation and systemic inflammation, improvement liver function, regression of ascites and hepatic encephalopathy, and an increase in serum sodium level.

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INTRODUCTION

Cirrhosis, which represents the culmination of chronic liver disease[1], is characterized by changes in liver morphology, reduced liver function, and the onset of portal hypertension. However, in addition to the liver, the intestine and its microbiota are affected by the pathophysiological derangements in cirrhosis. Cirrhosis is known to be associated with disturbances in the composition of the gut microbiota (gut dysbiosis[2-16]), expansion of the microbiota of the small intestine (small intestine bacterial overgrowth[17]), and increased permeability of the intestinal barrier[18], all of which result in bacterial translocation, which refers to the entry of bacteria and their components from the intestinal contents through the intestinal wall into the lymph, blood, and body tissues[19,20]. Bacterial translocation leads to systemic inflammation, which precipitates hemodynamic alterations [hyperdynamic circulation indicated by increased cardiac output and decreased systemic vascular resistance (SVR)] that contribute to liver decompensation[21-25]. This bidirectional association between the gut along with its microbiota and the liver is referred to as the gut-liver axis[26] or the gut-heart-liver axis[25]. Studies have shown that certain drugs that affect this axis can redress the hemodynamic imbalance and improve the clinical course in patients with cirrhosis. Among these drugs, probiotics are live microorganisms, which when administered in adequate amounts confer several health benefits on the host[27]. Although evidence-based research supports the role of probiotics in cases of hepatic encephalopathy, their effects on other symptoms and manifestations of cirrhosis remain unclear[28]. A non-controlled study reported that a 6-wk course of probiotics reduced the cardiac output and heart rate and increased the SVR and serum sodium levels in the study population[29].

Saccharomyces boulardii (*S. boulardii*), a probiotic yeast, has shown significant effectiveness for the treatment or prevention of diarrhea, inflammatory bowel disease, irritable bowel syndrome, *Helicobacter pylori* infection, and dyslipidemia, among other such conditions[30,31]. *S. boulardii* produces pleiotropic effects; it reestablishes the gut microbiome after dysbiosis[32], strengthens the intestinal immune barrier [33], improves the trophic function of gut microbiota[34], restores the impaired gut barrier, and protects against bacterial translocation[35] in experimental models and in patients with gut diseases. *S. boulardii*

administration in an experimental mouse model of cirrhosis led to correction of gut dysbiosis, decreased intestinal permeability, as well as reduced severity of liver inflammation and fibrosis[36]. However, the role of this probiotic is not known in humans with cirrhosis.

In this randomized placebo-controlled trial, we investigated the effect of probiotic administration (*S. boulardii*) on hemodynamic parameters, systemic inflammation, and complications of cirrhosis.

MATERIALS AND METHODS

Patients

In this single-blind randomized placebo-controlled trial, 198 consecutive patients with cirrhosis who underwent health check-ups at the Department of Hepatology's Clinic for Internal Diseases, Gastroenterology, and Hepatology at Sechenov University were screened for inclusion. The study procedures were explained to potential participants, and written informed consent was obtained before enrollment. The study was approved by the Ethics Committee of Sechenov University and was registered at clinicaltrials.gov (NCT05231772). The research protocol can be accessed from this website.

Inclusion criteria were as follows: (1) Diagnosis of cirrhosis based on histopathological, or clinical, biochemical, and ultrasonographic findings; (2) Child-Pugh class B or C cirrhosis; (3) Age between 18 years and 70 years; and (4) Signed informed consent. Exclusion criteria were as follows: (1) Administration of lactulose, lactitol, or other prebiotics, probiotics, antibiotics, or metformin during the 6 wk preceding study commencement; (2) Alcohol consumption 6 wk preceding study commencement; or (3) Diagnosis of inflammatory bowel disease, cancer, or any other serious disease.

There are no data to calculate the required sample size.

Of the 198 patients initially screened for inclusion, 40 met the inclusion criteria and were enrolled in the study (Figure 1). Patients included in the study were randomized into the test and control arms (ratio 1.5:1). The Excel function RANDBETWEEN (1:5) was used as a random number generator; for numbers 1 to 3, patients were assigned to the test arm and for numbers 4 or 5, patients were assigned to the placebo group. Patients who prematurely discontinued ingestion of the experimental probiotic/placebo or were administered antibacterial drugs, other probiotics, or prebiotics during the follow-up period were excluded from the study.

Intervention and controls

Patients in the test arm received *S. boulardii* at a dose of 250 mg twice a day for 3 mo and those in the control group received a placebo preparation at the same dose over the same period. Patients were not aware whether they were administered a placebo or the experimental drug. Additionally, all patients received standard of care treatment for cirrhosis. Drugs administered did not significantly differ between patient groups (Table 1). Patients were re-evaluated 3 mo after initiation of *S. boulardii* or placebo treatment.

Outcomes

All patients underwent a standard medical check-up for evaluation of cirrhosis and for measurement of indicators of systemic hemodynamics before and 3 mo after initiation of *S. boulardii* or placebo treatment (the first and second visit, respectively). There were no additional visits or examinations between these two time points. The outcomes included changes in cardiac output, SVR, the extent of systemic inflammation (represented by serum C-reactive protein levels), severity of ascites and hepatic encephalopathy, serum levels of liver biomarkers, and Child-Pugh scale scores.

Echocardiography was performed at rest based on the guidelines of the American Society of Echocardiography[37-40]. The systolic and diastolic blood pressure and heart rate were measured using an automatic oscillometric sphygmomanometer (A and D, Japan) simultaneously with measurement of the stroke volume. Table 2 shows the hemodynamic parameters calculated in this study[37-42].

The degree of ascites was determined based on the International Ascites Club scale as follows: 0 = No ascites; 1 = Minimal ascites (measurable only with instrumental methods); 2 = Clinically significant ascites (determined on physical examination); and 3 = Gross ascites[43].

The degree of hepatic encephalopathy was determined based on the following scale: 0 = No hepatic encephalopathy; 1 = Minimal hepatic encephalopathy; and 2 = Overt hepatic encephalopathy[44].

Statistical analysis

Statistical analysis was performed with STATISTICA 10 (StatSoft Inc., Tulsa, OK, United States) software. The data were presented as medians interquartile ranges]. Differences between continuous variables were assessed with the Mann-Whitney test because many variables were not distributed normally. Fisher's exact test was used to assess the differences between categorical variables. *P* values ≤ 0.05 were considered as statistically significant. We performed per-protocol analysis.

Table 1 Main indicators and drugs used of enrolled patients at inclusion by arms

	The test arm, <i>n</i> = 24	The control arm, <i>n</i> = 16	<i>P</i> value
Age, yr	48.5 (42.5-59.0)	53.5 (44.5-59.0)	0.730
Body mass index, kg/m ²	25.4 (22.3-27.9)	26.5 (24.3-28.7)	0.553
Male/female	8/16	9/7	0.134
Etiology of cirrhosis: Alcohol	12 (50.0)	8 (50.0)	> 0.050
Metabolically associated fatty liver disease	2 (8.3)	0	
HBV	2 (8.3)	0	
HCV	3 (12.5)	2 (12.5)	
Mixed	3 (12.5)	3 (18.8)	
Cryptogenic	2 (8.3)	3 (18.8)	
Child-Pugh score	9 (8-10)	9 (8-10)	0.730
Child-Pugh class, B/C	17/7	12/4	0.533
End-diastolic volume of the left ventricle, mL	109 (84-116)	100 (90-143)	0.689
Ejection fraction of the left ventricle, %	61.5 (59.4-62.8)	59.8 (57.5-62.0)	0.263
Stroke volume, mL	67 (52-72)	58 (55-82)	0.689
Heart rate, bpm	71 (69-75)	70 (69-74)	0.709
Cardiac output, L/min	4.8 (3.6-5.2)	4.4 (4.0-5.8)	0.473
Mean blood pressure, mmHg	84.7 (80.3-89.7)	87.3 (79.8-93.7)	0.499
Systemic vascular resistance, dyn · s · cm ⁻⁵	1442 (1243-1874)	1470 (1255-1744)	0.945
Mean pulmonary artery pressure, mmHg	23.4 (22.1-25.8)	23.4 (20.9-26.4)	0.749
Esophageal varices (Grade 1), <i>n</i> (%)	8 (33.3)	6 (37.5)	0.338
Esophageal varices (Grade 2-3), <i>n</i> (%)	16 (66.7)	7 (43.8)	
Minimal hepatic encephalopathy, <i>n</i> (%)	18 (75.0)	10 (62.5)	0.484
Overt hepatic encephalopathy, <i>n</i> (%)	2 (8.3)	2 (12.5)	
Hepatic encephalopathy, <i>n</i> (%)	20 (83.3)	12 (75.0)	0.399
Ascites, <i>n</i> (%)	22 (91.7)	12 (75.0)	0.160
Minimal ascites, <i>n</i> (%)	15 (62.5)	6 (37.5)	0.249
Clinically significant ascites, <i>n</i> (%)	7 (29.2)	6 (37.5)	
Red blood cells as 10 ¹² cell/L	3.7 (3.3-4.3)	3.6 (3.1-4.1)	0.689
White blood cells as 10 ⁹ cell/L	4.3 (3.2-5.6)	3.8 (2.6-7.2)	0.553
Platelets as 10 ⁹ cell/L	94 (69-107)	94 (48-104)	0.669
Serum total protein, g/L	73 (63-77)	70 (61-77)	0.649
Serum albumin, g/L	33 (31-36)	33 (29-37)	0.967
Serum total bilirubin, μmol/L	37 (27-64)	55 (29-67)	0.499
International normalized ratio	1.48 (1.39-1.68)	1.58 (1.31-1.73)	0.978
Serum cholesterol, mmol/L	4.1 (3.1-5.5)	3.5 (2.6-4.6)	0.230
Serum triglyceride, mmol/L	1.1 (0.7-1.4)	1.0 (0.7-1.4)	0.626
Serum creatinine, mg/dL	76 (65-88)	78 (70-105)	0.448
Serum sodium, mmol/L	140 (139-141)	141 (140-142)	0.235
Serum potassium, mmol/L	4.3 (4.0-4.8)	4.4 (4.1-4.6)	0.804
Serum glucose, mmol/L	4.7 (4.2-5.7)	4.8 (4.6-5.4)	0.464
Serum iron, μmol/L	13.9 (8.1-20.6)	11.3 (7.3-22.0)	0.761

Alanine aminotransferase, U/L	31 (20-46)	26 (20-51)	0.782
Aspartate aminotransferase, U/L	54 (34-72)	52 (38-79)	0.945
Gamma glutamyl transferase, U/L	82 (28-299)	84 (49-118)	0.934
Alkaline phosphatase, U/L	268 (221-395)	214 (173-274)	0.098
Cholinesterase, U/L	3650 (2861-3961)	3803 (2778-4215)	0.827
C-reactive protein, mg/L	9 (6-15)	7 (2-20)	0.347
Beta blockers, <i>n</i> (%)	17 (70.8)	11 (68.8)	0.580
Spirolactone, <i>n</i> (%)	22 (91.7)	14 (87.5)	0.529
Loop diuretics, <i>n</i> (%)	11 (45.8)	7 (43.8)	0.578
Ademetionine, <i>n</i> (%)	15 (62.5)	9 (56.3)	0.472
Entecavir or tenofovir, <i>n</i> (%)	2 (8.3)	0	0.354

HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 2 Calculations of hemodynamic parameters

Parameter	Calculation
End-diastolic and end-systolic volume of the left ventricle	Modified Simpson's disk method
Ejection fraction of the left ventricle	$[(\text{End-diastolic volume}) - (\text{end-systolic volume})] / (\text{end-diastolic volume})$
Stroke volume	$(\text{Doppler velocity time integral}) \times (\text{cross-sectional aorta area})$ [41]
Mean arterial pressure	$[(\text{systolic blood pressure}) + 2 \times (\text{diastolic blood pressure})] / 3$
Cardiac output	$(\text{Stroke volume}) \times (\text{heart rate})$
Systemic vascular resistance	$(\text{Mean arterial pressure}) / (\text{cardiac output})$
Systolic pulmonary artery pressure	$(\text{Right atrium pressure estimated from diameter of inferior vena cava and respiratory changes}) + 4 \times (\text{the peak velocity of the tricuspid valve regurgitant jet})^2$ [39,40]
Mean pulmonary artery pressure	$0.61 \times (\text{systolic pulmonary artery pressure}) + 2 \text{ mmHg}$ [42]

RESULTS

The study included 40 patients [24 (test group) and 16 (control group)] (Figure 1). No significant differences were observed between the groups at the time of study inclusion (Table 1). All included patients completed the study. None of the patients were hospitalized between the visits.

After a 3-mo course of the probiotic in comparison to the control group, we observed evidence of amelioration of hyperdynamic circulation (a decrease in cardiac output and end-diastolic volume and an increase in SVR) and systemic inflammation (a decrease in serum C-reactive protein levels), improved liver function (an increase in serum albumin and cholinesterase levels and a decrease in the value of Child-Pugh score), regression of ascites and hepatic encephalopathy, increased serum sodium levels, as well as a reduction in the severity of cholestasis (a decrease in serum alkaline phosphatase and serum gamma-glutamyl transpeptidase activity), and hypersplenism (an increase in platelet count). However, in contrast to patients in the test group, those in the control group showed an increase in mean blood pressure. No significant changes were observed in the levels of other variables, including in the grade of esophageal varices and the international normalized ratio (Table 3).

In the test arm, an improvement in liver function (a decrease in the value of Child-Pugh score: -2 [-3-(-1)] *vs* -0.5 [-1-0]; *P* = 0.042) and a decrease in the degree of ascites (-1 [-1-(-1)] *vs* 0 [0-0]; *P* = 0.015) was observed only in those patients (*n* = 18) who had a decrease in cardiac output after the course of the probiotic.

No patient developed acute-on-chronic liver failure and bleeding esophageal varices during the study, and no patient died during the study period.

Only 1 patient in the test arm developed self-limited itching as an adverse effect.

Table 3 Changes of the main indicators of the included patients after treatment

	The test arm (n = 24)	The control arm (n = 16)	P value
Body mass index, kg/m ²	-0.2 (-0.9-1.5)	0.0 (0.0-0.5)	0.281
Child-Pugh score	-1.5 [-3.0-(-0.5)]	0 (-0.5-1.5)	0.001
Child-Pugh class (from B or C to A), n (%)	8 (33.3)	1 (6.3)	0.048
End-diastolic volume of the left ventricle, mL	-13 [-17-(-10)]	0 (-3-12)	< 0.001
Ejection fraction of the left ventricle, %	0.5 (-0.7-0.3)	0.0 (0.0-0.3)	0.590
Stroke volume, mL	-7 [-12-(-4)]	0 (-3-8)	< 0.001
Heart rate, bpm	2 (-4-8)	-2 (-7-7)	0.234
Cardiac output, L/min	-0.5 [-1.0-(-0.1)]	0.3 (-0.3-0.9)	0.026
Mean blood pressure, mmHg	1.8 (-1.7-7.5)	3.8 (-3.3-15.3)	0.847
Systemic vascular resistance, dyn · s · cm ⁻⁵	237 (39-358)	30 (-200-227)	0.026
Mean pulmonary artery pressure, mmHg	0.0 (-2.1-0.6)	1.2 (0.0-1.8)	0.043
Esophageal varices, a decrease in grade, n (%)	2 (4.3)	0	0.354
Esophageal varices, an increase in grade, n (%)	0	0	-
Regression hepatic encephalopathy, n (%)	8 (33.3)	1 (6.3)	0.048
Ascites, a decrease in degree, n (%)	15 (62.4)	4 (25.0)	0.022
Ascites, an increase in degree, n (%)	1 (4.2)	3 (18.8)	0.167
Red blood cells as 10 ¹² cell/L	0.2 (-0.1-0.5)	0.2 (-0.1-0.4)	0.730
White blood cells as 10 ⁹ cell/L	0.1 (-1.2-0.6)	-0.1 (-2.1-0.7)	0.782
Platelets as 10 ⁹ cell/L	11 (4-32)	-6 (-14-1)	< 0.001
Serum total protein, g/L	-0.2 (-4.2-8.9)	-1.4 (-3.5-5.6)	0.793
Serum albumin, g/L	3.0 (0.6-7.7)	-3.1 (-5.1-2.4)	0.001
Serum total bilirubin, μmol/L	-5.1 [-23.9-(-0.9)]	-3.7 (-10.0-17.2)	0.181
International normalized ratio	0.0 (-0.1-0.1)	0.0 (-1.0-0.1)	0.544
Serum cholesterol, mmol/L	0.2 (-0.4-1.2)	0.5 (-1.0-2.0)	0.571
Serum triglyceride, mmol/L	0.1 (-0.2-0.2)	0.1 (-0.6-0.4)	0.836
Serum creatinine, mg/dL	2.4 (-9.1-8.1)	-3.5 (-11.2-4.2)	0.264
Serum sodium, mmol/L	1.5 (0.5-3.0)	-1 (-3-2)	0.048
Serum potassium, mmol/L	0.0 (-0.4-1.2)	0.1 (-0.2-0.3)	0.523
Serum glucose, mmol/L	0.4 (-0.1-0.7)	0.0 (-0.9-0.8)	0.423
Alanine aminotransferase, U/L	-1 (-15-6)	2 (-15-8)	0.740
Aspartate aminotransferase, U/L	-9 (-32-1)	-2 (-26-20)	0.116
Gamma glutamyl transferase, U/L	-8 (-171-11)	6 (-15-23)	0.039
Alkaline phosphatase, U/L	-40 (-95-3)	26 (-57-91)	0.016
Cholinesterase, U/L	257 (28-734)	-155 [-239-(-68)]	0.016
C-reactive protein, mg/L	-3.0 [-4.5-(-0.5)]	1.0 (-2.0-4.5)	0.044

DISCUSSION

This is the first randomized controlled study that investigated the effect of probiotics on hemodynamic disturbances in patients with cirrhosis. Our results concur with those reported by a previous uncontrolled study[29], which showed that these drugs reduce cardiac output and increase SVR. In our study, the reduced cardiac output was attributable to a decrease in the end-diastolic volume, which may indicate a reduction in the effective circulating blood volume.

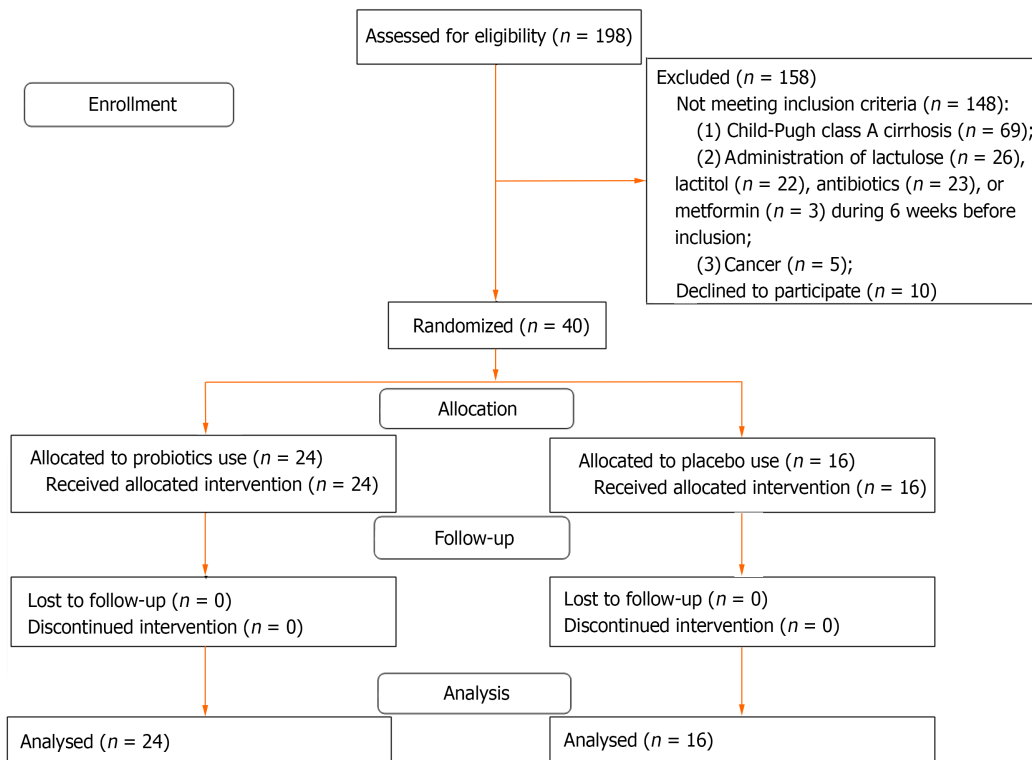


Figure 1 CONSORT 2010 flow diagram.

The use of the probiotic also increased serum albumin and sodium levels and decreased in the degree of ascites. We assume that the probiotics inhibit bacterial translocation and thereby ameliorate hyperdynamic circulation, with a consequent reduction in the degree of ascites, which corrects hypoalbuminemia and hyponatremia. Unfortunately, we could not evaluate the indicators of intrahepatic hemodynamics (for example, the hepatic venous pressure gradient, among other variables).

Interestingly, this study highlights that probiotics reduced serum levels of biomarkers of cholestasis (alkaline phosphatase and gamma-glutamyl transpeptidase). This is the first study to report these findings; further studies are warranted to investigate the mechanisms underlying these changes. We observed probiotic-induced reduction in the severity of hepatic encephalopathy, which is consistent with the results reported by previous research[28]. In our study, probiotic ingestion did not affect the degree of esophageal varices and prothrombin levels (indicated by the international normalized ratio); our results were consistent with those reported by a previous study[28].

Probiotic use was associated with a significant improvement in liver function in our study; 33.3% of patients in the probiotic arm and only 6.3% of patients in the control arm showed Child-Pugh class A cirrhosis after a course of probiotic or placebo administration. We observed no significant probiotic-induced adverse effects during the study. Overall, our study showed that probiotic administration may be a useful therapeutic strategy for correction of gut-heart-liver axis disturbances.

This is the first randomized placebo-controlled trial that confirms the role of probiotics in amelioration of hemodynamic disorders in cirrhosis, together with improvement in levels of several liver biomarkers, which serves as a strength of our study.

A limitation of our study is the fact that biomarkers of bacterial translocation and intestinal permeability, biomarkers of systemic inflammation in addition to C-reactive protein, as well as indicators of intrahepatic hemodynamics were not evaluated. Further research is warranted to overcome this challenge.

CONCLUSION

Probiotic administration was associated with amelioration of hyperdynamic circulation and the associated complications of cirrhosis.

ARTICLE HIGHLIGHTS

Research background

Bacterial translocation exacerbates the hyperdynamic circulation observed in cirrhosis and contributes to a more severe disease course.

Research motivation

Probiotics may reduce bacterial translocation and may therefore be useful to redress the circulatory imbalance.

Research objectives

To investigate the effect of probiotics on hemodynamic parameters, systemic inflammation, and complications of cirrhosis in this randomized placebo-controlled trial.

Research methods

This single-blind randomized placebo-controlled study included patients with Child-Pugh class B and C cirrhosis that received probiotics (*Saccharomyces boulardii*) or a placebo for 3 mo. Liver function and the systemic hemodynamic status were evaluated pre- and post-intervention. Echocardiography and simultaneous blood pressure and heart rate monitoring were performed to evaluate systemic hemodynamic indicators. Cardiac output and systemic vascular resistance were calculated.

Research results

Following a 3-mo course of probiotics in comparison to the control group, we observed amelioration of hyperdynamic circulation and systemic inflammation with improved liver function, reduction in the severity of ascites, hepatic encephalopathy, and cholestasis, and an increase in platelet counts.

Research conclusions

Probiotic administration was associated with amelioration of hyperdynamic circulation and the associated complications of cirrhosis.

Research perspectives

To study the changes in the levels of the biomarkers of bacterial translocation, intestinal permeability, and in indicators of intrahepatic hemodynamics after the use of the probiotic in decompensated cirrhosis.

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FOOTNOTES

Author contributions: Ivashkin V provided the research idea; Ivashkin V, Efremova I, and Roman Maslennikov R designed the study; Efremova I and Maslennikov R wrote the draft; Maslennikov R was the guarantor; All authors edited the draft and contributed to the research and data analysis.

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Country/Territory of origin: Russia

ORCID number: Roman Maslennikov 0000-0001-7513-1636; Irina Efremova 0000-0002-4112-0426; Vladimir Ivashkin 0000-0002-6815-6015; Maria Zharkova 0000-0001-5939-1032; Elena Poluektova 0000-0002-9038-3732; Elena Shirokova 0000-0002-6819-0889; Konstantin Ivashkin 0000-0002-5699-541X.

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