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Oral booster probiotic bifidobacteria in SARS-COV-2 patients

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Abstract

Oral booster-single strain probiotic bifidobacteria could be a potential strategy for SARS-CoV-2. This study aims to evaluate the role of oral probiotic *Bifidobacterium* on moderate/severe SARS-CoV-2 inpatients. In this single-center study, we analyzed data of 44 moderate/severe inpatients with diagnosed COVID-19 in Istanbul Maltepe University Medical Faculty Hospital, 2020 from 1 November 2020 to 15 December 2020. Clinical and medication features were compared and analyzed between patients with or without probiotic. In result, 19 of the 44 patients (43.18%) who were administrated with oral booster-single strain probiotic were discharged with the median inpatient day of 7.6 days which were significantly shorter than those of patients without probiotic. There were significant differences in inpatient days, radiological improvement at day 6 and week 3, and reduction in interleukin-6 levels in those receiving oral probiotic therapy. Although the mortality rate was 5% in the probiotic group, it was 25% in the non-probiotic group. Booster-single strain probiotic bifidobacteria could be an effective treatment strategy for moderate/severe SARS-CoV-2 inpatients to reduce the mortality and length of stay in hospital.

Keywords

SARS-CoV-2, probiotic, bifidobacteria

Introduction

SARS-CoV-2 is a pandemic virus that exists itself with lung disease as well as leading to symptoms and signs associated with the gastrointestinal tract. It is especially manifested by the disturbed immune status in lung and intestinal tissues. Although the pathophysiology of the SARS-CoV-2 in lung and gut remains to be defined, it is evident that its pathological impacts include both direct effects of viral invasion and a complex immunological response.[1] Increased endoplasmic reticulum stress and cellular autophagy, which play key roles for the cellular replication of the virus, are mediated by the enhanced adaptive Th17/IL-6 immune system and this leads to an uncontrolled immune response.[2] Currently, there are no proven medical treatment developed for this uncontrolled immune response. Anti-inflammatory agents (corticosteroids), anticoagulation agents (enoxaparin), Favipiravir (antiviral treatment), and specific immune treatment (Anti-Il-6, anti-Il-1, and Immune plasma) are considered for the medical therapy of moderate/severe SARS-CoV-2 inpatients in the Turkish Health of Ministry guidelines for COVID-19.[3]

Probiotics are living microorganisms that have been shown to have modulatory effects on adaptive immunity. The beneficial immune modulation effects of some single strain probiotic bacteria have been shown.[4] The pathogenesis of the immune response to coronavirus bears a strong resemblance with TH17-Th1driven autoimmune diseases and these TH17-Th1 immune interactions appear

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to play an important role in virus replication. The immune beneficial effects of bifidobacteria strains include an anti-IL-17 effect which could play important role in SARS-CoV-2 treatment.[2] *Bifidobacterium animalis sp. Lactis* provides to rapid mucosal healing in inflammatory bowel disease (IBD) and this effect was related to the IL-17 inhibitory effect of the *Bifidobacterium animalis sp. Lactis* strain.[2,4] Cytokine storm can be controlled through these immune modulating effects of probiotic bifidobacteria. In a current analysis, it has been shown that reduced Bifidobacterium abundance is likely associated with increased SARS-CoV-2 infection severity,[5] so Bifidobacterium and other probiotic supplementation or refloralization *via* booster Bifidobacterium administration might provide a therapeutic benefit, particularly for patients hospitalized with severe disease. Here, we offer a new approach with booster dose oral single strain probiotic Bifidobacterium administration in moderate/severe SARS-CoV-2 patients.

Method

Patients

In this retrospective study, 44 moderate/severely ill adult inpatients (≥18 years old), who were admitted to Istanbul Maltepe University Medical Faculty Hospital, the designated hospital for Covid-19 patients, 2020 from 1 November 2020 to 15 December 2020 have been included. The patients were confirmed as COVID-19 positive according to World Health Organisation guidance, and for non-probiotic group, the treatment was given according to Turkish Health Ministry guidelines for COVID-19. It has been scanned retrospectively from the hospital registry system in accordance with the Helsinki Declaration Principles. The patients were followed up to 15 January 2021.

Medication

In this retrospective study, 44 moderate/severely ill adult inpatients (≥18 years old), who were admitted to Istanbul Maltepe University Medical Faculty Hospital, the designated hospital for Covid-19 patients, 2020 from 1 November 2020 to 15 December 2020 have been included. The inpatients were divided into probiotic group (*n*:20) and nonprobiotic (*n*:24) group. The probiotic group consisted of those who deny and do not tolerate the (Tables 1 and 2) Ministry of Health guide treatment for SARS-CoV-2. Oral administration of probiotic treatment included one trillion CFUs *Bifidobacterium* BB-12 strain which were dissolved in 250 mL water. Total dose were divided into three parts and administrated to patients for 3 days. Inpatient groups were not consumed probiotic-containing foods or any other probiotic supplements during hospitalization.

Additional treatment included the following levofloksasin in probiotic group, ceftriaxone-meropenem in non-probiotic group and specific treatment (Anti-Interleukin-6, Anti-Interleukin-1, and Immune plasma) in non-probiotic group.

Procedures

The clinical features, medical therapy, and laboratory findings of diagnosed moderate/severe cases of SARS-CoV-2 were collected from hospital electronic medical records. The diagnosis of SARS-CoV-2 is to confirm real-time reverse-transcriptase polymerase-chain-reaction (RTPCR) assay tests using throat-swab specimens that were obtained from upper respiratory tracts after clinical symptoms of fever, cough, and dyspnea.

The lung disease severity of SARS-CoV-2 was defined according to the clinical and thorax CT radiological criteria:

Moderate Disease/Pneumonia: Patients who describe shortness of breath in addition to clinical findings, SpO> 90 and above, need intermittent nasal oxygen and with ground-glass, uncommon local, or multi-focal infiltration findings on tomography.

Severe Disease/Pneumonia: In addition to clinical findings, patients with significant shortness of breath, SpO: <90 and in need of oxygen with a continuous nasal and/or mask, and diffuse ground-glass in tomography, diffuse multi-focal infiltrations and consolidated areas.

The specific treatment consists of monoclonal antibodies [anti-Il-6 (TCZ), anti-Il-1] and immune plasma therapies. According to Turkish management guidelines for COVID-19, Oral Favipiravir treatment 2000 mg/total dose in Mild/Moderate inpatients and specific treatment who does not respond the Favipiravir treatment in Moderate/Severe inpatients was given non-probiotic group.

Thoracic tomography was taken on hospital admission, on the sixth day and 3 weeks after hospitalization. Radiological improvement was considered as significant improvement in lung condition with regression of diffuse airspace consolidations, ground-glass opacities and septal thickening.

Plasma levels of interleukin-6 were collected after hospitalization and at 3 weeks.

The criteria for discharge were considered; absence of fever for at least 3 days, substantial improvement in both lungs on chest CT, clinical remission of respiratory symptoms, and two throat-swab samples negative for the SARS-CoV-2 test obtained at least 24 h.

Statistical analysis

Chi-square independence test was used to get the dependency relation between variables which are at nominal and/or ordinal scale. If the prerequisite of chi-square independence test was not provided, fisher exact test used for 2*2 contingency tables. To test the mean equality for two groups, Man–Whitney U test was used because of normality condition. Frequency distribution,

Table 1. Clinical features of non-probiotic group.

Moderate (M) and severe(S) pneumonia	Steroid and LWMAH	Hospitalization period (Day)	Specific treatment (Sp) (anti-IL-1,Anti-IL-6,Plazma)	Sp treatment type	Sp. Treatment type	Sp.treatment type	Antibiotic	Antibiotic type	Antibiotic type	Dead	Thorax CT resolution 6 day of hospitalization	Thorax CT resolution on 3 weeks	Hospitalization IL-6 levels (pg/ml)	3 weeks ıl-6 level
M	Yes	14	No				No			No	No	No	80	50
M	Yes	13	No				No			No	No	No	58	N/A
M	Yes	11	No				No			No	Yes	Yes	36	15
S	Yes	12	Yes	Tocilizumab			Yes	Ceftriaxone		No	No	N/A	77	36
M	Yes	14	No				No			No	No	Yes	48	10
S	Yes	10	Yes	TCZ			Yes	Meropenem		No	No	N/A	35	N/A
S	Yes	10	No				Yes	Gentamycine		No	No	N/A	64	N/A
S	Yes	10	No				Yes	Ceftriaxone		No	No	No	44	24
S	Yes	14	Yes	TCZ	Anti-IL-1	Plasma	Yes	Ceftriaxone	Meropenem	No	No	No	96	46
M	Yes	13	No				Yes	Ceftriaxone		No	Yes	No	84	28
S	Yes	12	Yes	TCZ			Yes	Ceftriaxone		No	No	No	45	36
S	Yes	11	Yes	TCZ	Anti-IL-1		Yes	Ceftriaxone		No	No	N/A	63	N/A
S	Yes	22	Yes	TCZ			No			No	No	No	180	N/A
S	Yes	10	Yes				No			No	Yes	Yes	106	16
S	Yes	13	Yes	İmmun plazma			Yes	Ceftriaxone	Meropenem	Yes	No	N/A	74	N/A
S	Yes	23	Yes	TCZ			Yes	Meronem		Yes	No	N/A	256	N/A
M	Yes	11	Yes	Anti-IL-1			Yes	Ceftriaxone		Yes	No	N/A	127	N/A
S	Yes	17	Yes	TCZ	ACT	Plasma	Yes	Ceftriaxone	Meropenem	Yes	No	N/A	345	N/A
S	Yes	14	Yes	TCZ	ACT		Yes	Ceftriaxone		Yes	No	N/A	156	N/A
S	Yes	17	No				Yes	Meronem		No	No	No	106	60
S	Yes	10	Yes	Anti-IL-1			Yes	Ceftriaxone		No		No	62	36
S	Yes	8	Yes	ACT			Yes	Ceftriaxone		No	No	Yes	24	4
S	Yes	24	Yes	Anti-IL-1			Yes	Ceftriaxone	Meropenem	No	No	No	124	76

Table 2. Clinical features of probiotic group (N/A: Not applicable).

Treatment case group	Gender	Age	Moderate and severe pneumonia	Steroid and LWMAH	Hospitalization period (Day)	Specific treatment (Sp) (anti-IL-1,Anti-IL-6,Plazma)	Antibiotic	Antibiotic type	Dead	Thorax CT resolution 6 days of hospitalization (posttreatment 3 day)	Thorax CT resolution on 3 weeks	Hospitalization IL-6 levels (pg/ml)	3 weeks ıl-6 level
1	F	45	Moderate	Yes	7	No	No		No	Yes	Yes	62	5
2	F	47	Moderate	Yes	6	No	No		No	Yes	Yes	79	7
3	M	51	Moderate	Yes	7	No	No		No	Yes	Yes	27	3
4	F	36	Severe	Yes	8	No	Yes	Levofloksasin	No	Yes	Yes	156	4
5	M	41	Moderate	Yes	6	No	No		No	Yes	Yes	124	7
6	M	71	Severe	Yes	9	No	Yes	Levofloksasin	No	Yes	N/A	78	N/A
7	F	60	Moderate	Yes	7	No	No		No	No	N/A	56	N/A
8	F	61	Severe	Yes	8	No	Yes	Levofloksasin	No	No	Yes	188	8
9	F	45	Moderate	Yes	9	No	Yes	Levofloksasin	No	Yes	Yes	94	4
10	M	66	Moderate	Yes	7	No	Yes	Levofloksasin	No	Yes	Yes	116	6
11	M	44	Moderate	Yes	6	No	No		No	Yes	Yes	246	6
12	F	50	Moderate	Yes	6	No	No		No	Yes	N/A	135	N/A
13	F	50	Severe	Yes	9	No	Yes	Levofloksasin	Yes	No	N/A	486	N/A
14	M	65	Severe	Yes	8	No	No		No	No	Yes	106	10
15	F	45	Moderate	Yes	7	No	Yes		No	Yes	N/A	55	N/A
16	M	44	Moderate	Yes	7	No	Yes		No	Yes	N/A	79	N/A
17	M	73	Moderate	Yes	8	No	Yes	Levofloksasin	No	Yes	N/A	24	N/A
18	M	55	Severe	Yes	9	No	Yes	Levofloksasin	No	No	Yes	110	9
19	M	49	Moderate	Yes	8	No	Yes		No	Yes	Yes	56	6
20	M	73	Severe	Yes	9	No	Yes	Levofloksasin	No	No	Yes	88	5

Percentage was used as descriptive statistics for nominal and ordinal scale variables. Mean, standard deviation, and frequency were used as descriptive statistics for interval/ratio scale variables. SPSS Version 25 were used for analysis. Power of test was calculated as post-hoc.

Results

Outcome

This retrospective single-center study analyzed 44 moderate/severe inpatients with SARS-CoV-2 who were hospitalized in Istanbul Maltepe University Medical Faculty Hospital 2020 from 1 November 2020 to 15 December 2020. The clinical features were followed up to 15 January 2021. In result, 19 of the 20 patients (95%) who were treated with probiotic discharged with the median inpatient day of 7.6 days and lower mortality rate 5%. 19 of the 24 (79%) patients without the treatment of probiotic discharged with the median inpatient day of 13.6 days and higher mortality rate 20.83%. Significant differences existed across the treatment of probiotic with regards to inpatient days ($p < 0.001$), sixth day and at 3 weeks radiological improvement ($p < 0.001$) and decrease in interleukin-6 levels ($p < 0.001$). No adverse event was observed in probiotic group.

Clinical features

Probiotic and non-probiotic groups. Since the number of successful treatment for death rates is below 5, independent samples t test could not be performed for rates. The chi-square test could not be performed because the ratio of cells with an expected value less than five is more than 50%. According to Fisher Exact test results in 2 * 2 tables, the death status was not dependent on the group (Chi-square = 2.497, df = 1, $p = 0.192$). Although the tests used for group comparisons cannot be used due to sample size and Fisher's exact test results do not show dependence, the mortality rate in the treatment group is one fourth of the control group (Table 3).

Inpatient day

Hospitalization period (Day) values differ at 99% confidence level between control and treatment groups (μNonprobiotic=13.6, μProbiotic=7.6, $p = 0.000$) (Table 4).

Thoracic findings

Thorax CT resolution on 6 days of hospitalization (Post-treatment 3 day for probiotic group) results are dependent on treatment groups at 99% confidence level (Table 5). Although the early response rate was 13.6% in the nonprobiotic group, this rate increased to 70.0% in the probiotic group.

Thorax CT resolution on 3 weeks results are dependent on groups at 99% confidence level. Although the response rate was 28.6% in the nonprobiotic group, this rate increased to 100.0% in the probiotic group (Table 6) (Figures 1 and 2).

Plasma levels of interleukin-6

Third week's plasma Il-6 level values differ at 99% confidence level between control and treatment groups (μNonprobiotic = 33.6, μProbiotic = 6.2, $p = 0.000$) (Table 7).

Discussion

In current, there is no specific anti-viral medical therapy for SARS-CoV-2,[6] and often supportive treatments are considered. Probiotics could be considered as a therapy for SARS-CoV-2.[2,7–9] However, there is a lack of scientific report about the effect of single strain probiotic bacteria on SARS-CoV-2. In our study, we evaluated 44 moderate/severe SARS-CoV-2 inpatients, providing clinical evidence that single strain probiotic bifidobacteria can reduce mortality and hospital stay in moderate/severe SARS-CoV-2 patients. Early resolution in thorax CT and decrease in interleukin six level can be predictors of healing.

SARS-CoV-2 causes Endoplasmic Reticulum (ER) stress condition leads to the inositol-requiring enzyme 1(IRE1) pathway[2] mediated autophagy. In a report, viral replication could be decreased by blocking the inositol-requiring enzyme one in SARS-CoV patients with bronchitis.[10] Also, Kong et al.[11] showed that IL-6 induces autophagy *via* the IRE1. Interleukin-17 is a proinflammatory cytokine that reveals an important role in the adaptive immune system. IL-17 (originating mainly from Th17) is also a strong cytokine by increasing of ER stress and autophagy via IRE1.[4] Besides these, IL-17 plays a potent inducer of chronic inflammation in IBD.[4] Hou et al.[12] reported that the increasing of IL-6 stimulates the production of Th17 cells and that IL-6 and IL-17 association promotes the viral replication and this synergistically communication could be important therapeutic strategy for SARS-CoV therapies. Increased IL-6 levels were reported in patients with SARS and were correlated with disease severity.[13] Zhou et al.[14] showed that IL-6 levels were correlated with mortality in patients with SARS-CoV-2. The over expression of IL-6 might explain the excessive activated Th17/Il-17 cells observed in SARS-CoV-2 patients.[15] Grifoni et al.[16] cited that blood IL-6 level at hospital admission might be considered as a predictive factor for the combined endpoint progression to moderate/severe disease and/or in-hospital mortality, and it seems to be the best prognostic factor for negative outcome. Although cytokine storm occurred due to the uncontrolled adaptive immune response that occurs during the virus cell invasion and cellular replication, treatment responses could not be shown with specific anti-interleukin treatments. Rosas et al. showed that there is no effect of anti-interleukin

Table 3. Mortality rate in non-probiotic and probiotic group (p = 0.192) power 0.185.

Dead * group Crosstabulation					
			Group		
			Non-probiotic	Probiotic	Total
Dead	Yes	Count	5	1	6
		% Within group	21.7%	5.0%	14.0%
	No	Count	18	19	37
		% Within group	78.3%	95.0%	86.0%
Total		Count	23	20	43
		% Within group	100%	100%	100%

Table 4. Inpatient days in probiotic and non-probiotic group (p < 0.001) power 0.999.

Group		N	Mean	Std. Deviation	Std. Error mean	Man UZ	p
Hospitalization period (Day)	Non-probiotic	23	13.6	4.34	0.90	7500	0.000
	Probiotic	20	7.6	1.10	0.25	−5447	

Table 5. Early thoracic findings in probiotic and non-probiotic group (p < 0.001) power 0.964.

Crosstab					
			Group		
			Non-probiotic	Probiotic	Total
Thorax CT resolution 6 days of hospitalization (Posttreatment 3 day)	Yes	Count	3	14	17
		% Within group	13.6%	70.0%	40.5%
	No	Count	19	6	25
		% Within group	86.4%	30.0%	59.5%
Total		Count	22	20	42
		% Within group	100%	100%	100%

six treatment on mortality and morbidity in SARS-CoV-2 patients.[17] Also, Cavalli et al. presented that interleukin-1 inhibition has no effect on disease mortality and morbidity.[18]

There are currently limited scientific studies with probiotics in SARS-CoV-2. Li et al. reported that oral probiotics might be an effective therapeutic approach for the treatment of SARS-CoV-2 patients to reduce the secondary infection and modulated the adaptive immunity.[19] In accordance to Santacroce et al.[20] probiotics might have an important role against the SARS-CoV-2 infection. Some strains of Bifidobacterium such as BB-12, Infantis show anti- IL-17 effect. A booster-single dose administration of Bifidobacterium strain such as BB-12, Infantis might be considered as a therapeutic method in SARS-CoV-2 patients.[2] *Bifidobacterium animalis* might provide blocking the replication of SARS-CoV by reducing ER stress-related autophagy over the anti-interleukin-17 effect. Oral booster dose administration of *Bifidobacterium animalis* subsp. *Lactis* in SARS-CoV-2 patients' effectiveness on intestinal and lung recovery could be attributed to the enhancement/control of immune modulatory status and possible anti-IL-17/IL six effect in intestinal mucosa. *B. animalis* subsp. *Lactis* BB-12 does not belong to the human gut microbiota system. However, BB-12 strain has been reported to be effective and safe for human intestinal microbiota.[21] Also, BB-12 strain shows strong growth ability under gastric pH and bile acid conditions.[22] Larsen et al showed that the dysbiosis recovery of BB-12 increased significantly with increasing dose.[23] According to them, up to 10^{12} CFU of *Bifidobacterium BB-12* can be considered as a booster dose. Some of single strain probiotic bifidobacteria such as

Table 6. Thorax CT resolution results at week three in probiotic and non-probiotic group ($p<0.01$) power 0.998.

Crosstab

			Group		
			Non-probiotic	Probiotic	Total
Thorax CT resolution on 3 weeks	Yes	Count	4	13	17
		% Within group	28.6%	100.0%	63.0%
	No	Count	10	0	10
		% Within group	71.4%	0.0%	37.0%
Total		Count	14	13	27
		% Within group	100%	100%	100%

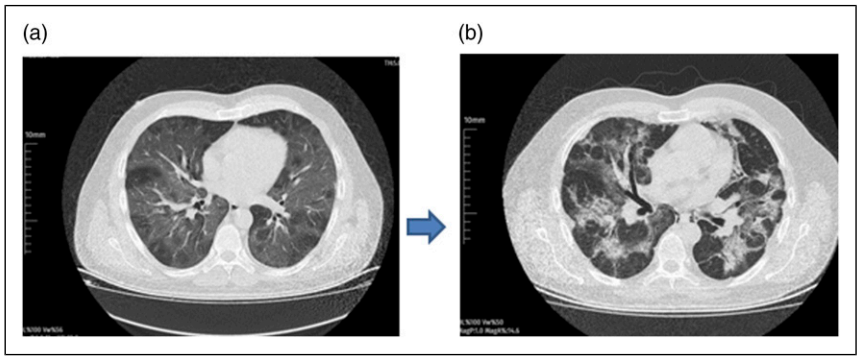

Figure 1. Non-probiotic case with severe disease thorax CT at hospital admission (a) and at 3 weeks (b).

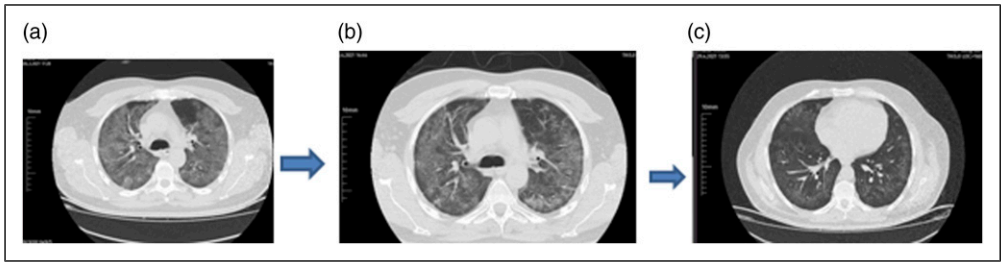

Figure 2. Probiotic case with severe disease thorax CT at hospital admission (a), on sixth day of hospitalization (posttreatment 3th day) (b) and at 3 weeks (b).

Table 7. Plasma Il-6 levels in probiotic and non-probiotic group ($p=0.000$) power 0.993.

Group		N	Mean	Std. Deviation	Std. Error mean	Man U Z	*p*
3 weeks ıl-6 level	Non-probiotic	13	33.6	20.71	5.74	11,50000	0.000

BB-12, Infantis have an anti-viral exopolysaccharide cell feature that can block SARS-CoV-2 adhesion on tissue. Baindara et al.[24] cited that *Lactobacillus casei* and Bifidobacterium lactis probiotics have anti-viral activity against the respiratory viral diseases. Although it has been shown that probiotics containing multiple species taken from the mouth reduce the severity of the infection,[20] the cause and effect relationship cannot be clearly revealed due to the various of probiotic bacterial species, at this point, the high dose single strain of probiotic bifidobacteria approach maybe more suitable method. However, our study group was small and our initial results must further be supported by large randomized studies. There is also a need for more comprehensive analytic calculation studies by confirming gut microbial analysis methods in those with dysbiosis in large t randomized studies

Conclusion

Oral booster dose *Bifidobacterium animalis* subsp. *Lactis* administration could provide lower mortality, shortening the length of stay in hospital, early radiologic improvement and decrease plasma IL-6 level in moderate/severe SARS-CoV-2 patients. It is still necessary to develop diagnostic strategies to determine the patients to whom this method would be the most applicable.

Declaration of Conflicting Interests

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