Original Article

Iran J Pediatr
Dec 2013; Vol 23 (No 6), Pp: 669-674

Effects of Probiotics on Quality of Life in Children with Cystic Fibrosis; A Randomized Controlled Trial

Seyed-Ali Jafari[1], MD; Atieh Mehdizadeh-Hakkak[*2], MD; Hamid-Reza Kianifar[3], MD; Paria Hebrani[4], MD; Hamid Ahanchian[5], MD; Elaheh Abbasnejad[1], MD

1. Department of Pediatric Gastroenterology, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
2. Cystic Fibrosis Clinic, Dr. Sheikh Pediatric Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
3. Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
4. Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
5. Department of Pediatric Immunology and Allergy, Mashhad University of Medical Sciences, Mashhad, Iran

Received: *Feb 16, 2013*; Accepted: *Sep 02, 2013;* First Online Available: *Nov 27, 2013*

Abstract

Objective: Patients with cystic fibrosis (CF) usually have abnormal intestinal microbiota and dysregulated immune mediators due to massive exposure to antibiotics. Probiotics as immunomodulatory and anti-inflammatory substances are considered to improve both clinical and biochemical intestinal and pulmonary function in CF patients. We decided to investigate the effects of probiotics on quality of life and pulmonary exacerbations in children with cystic fibrosis.

Methods: In a prospective, randomized, controlled clinical trial, 37 CF patients (2-12 years old) were randomly divided into two groups. 20 patients of probiotic group took probiotics (2×10^9CFU/d) for one month while 17 patients of control group took placebo capsules. Quality of life was determined using PedsQL™4.0 questionnaire at the beginning, then three and six months after completing the treatment period. Rate of pulmonary exacerbation in probiotic group patients was also evaluated during three months after intervention and compared to the same three months of the previous year. Results were analyzed using SPSS (11.5). $P<0.05$ was considered statistically significant.

Findings: Significant improvement was observed in the mean total score of parent reported quality of life among probiotic group patients in comparison with placebo group at 3rd month ($P=0.01$), but this was not significant at 6th month of probiotic treatment. Rate of pulmonary exacerbation was significantly reduced among probiotic group ($P<0.01$).

Conclusion: Probiotics are considered as useful nutritional supplements on reducing number of pulmonary exacerbations and improving quality of life in patients with cystic fibrosis. Effects of probiotics seem to be temporary and probably continuous ingestion might have more stable improving effects on quality of life.

Iranian Journal of Pediatrics, Volume 23 (Number 6), December 2013, Pages: 669-674

Key Words: Cystic Fibrosis; Probiotics; Quality of Life; Pulmonary Exacerbation

Introduction

Progressive inflammatory lung disease, characterized by recurrent destructive airway infection, is the main cause of mortality, morbidity and impaired quality of life in patients with cystic fibrosis (CF), resulting in respiratory failure in 90% of patients. Efforts to decrease pulmonary exacerbation expose patients to heavy load of antibiotic therapy which leads to alteration of

*** Corresponding Author;**
Address: Number 21, 12th Felestin Street, Mashhad, Iran
E-mail: aty_mehdizadeh@yahoo.com

microbiota and dysregulation of immune mediators[1-3].

Intestinal inflammation is another typical feature of cystic fibrosis, mainly due to constant exposure to wide spectrum of antibiotics and different medications. This is documented by increased concentration of fecal calprotectin and production of rectal nitric oxide, suggesting a constant intestinal inflammatory state. In addition, the intestinal permeability is increased in CF patients, leading to impaired intestinal barrier function[4,5].

Probiotics are live micro-organisms which are colonized in the intestine, reduce intestinal inflammation, and improve both clinical and biochemical intestinal functions in CF patients[6,7]. Probiotics have been successfully used in childhood gastroenteritis, atopic disorders and *Helicobacter pylori* infection[8-10]. There are evidences that probiotic supplementation decreases the rate of pulmonary exacerbation and hospital admission in CF patients[11,12]. What probiotics do is chiefly through their effect on intestinal permeability and immune response modification[13].

On the other hand, it has been repeatedly indicated that rehabilitation programs and treatments which target respiratory inflammation and maintenance of a good nutritional status are responsible for improvement of quality of life in CF patients[14,15]. Recently, quality of life evaluation is becoming an important criterion of disease status and treatment outcome among patients with chronic illnesses such as cystic fibrosis.

According to chronic lung inflammation in CF patients and the immunoregulatory, anti-inflammatory roles of probiotics, together with the effect of pulmonary status on quality of life, an assumption raises that probiotic supplementation may have beneficial impact on preventing pulmonary deterioration, therefore, improving quality of life in patients with cystic fibrosis.

Current study investigated the effects of a commercially available multi-microbial probiotic supplementation on quality of life and pulmonary exacerbation in children with cystic fibrosis through a randomized, controlled clinical trial.

Subjects and Methods

A randomized clinical trial was performed in Dr. Sheikh Pediatric Hospital CF clinic, Mashhad, Iran. Sample size measurements by NCSS suggested a minimum number of 14 patients for each probiotic and placebo groups. In current study 37 CF patients (20 cases and 17 controls) with positive sweat test (Cl^->60 meq/l) were enrolled in this study.

Pancreatic insufficiency was a common feature of all patients diagnosed by clinical symptoms and signs such as steatorrhea, malabsorption, fat-soluble vitamin deficiency, rectal prolapse, and growth failure. Inclusion criteria were as following: (1) aged 2-12 years, (2) absence of other chronic illnesses rather than CF, (3) accepting the informed consent by parents. Exclusion criteria were congenital heart disease and CNS abnormalities. The study proposal was approved by Ethics Committee of Mashhad University of Medical Sciences. Informed consent was taken from all parents.

Patients were randomly divided into two groups of probiotic and placebo. 20 patients of probiotic group were assigned to take probiotics for one month and 17 patients of placebo group took placebo capsules which contained all ingredients of probiotic capsules except the effective substance. Probiotics were used as commercially available capsules (Protexin®, Probiotics International Company, U.K.), two capsules per day for one month, each containing 10^9 CFU bacteria: *Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifido-bacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, and Lactobacillus bulgaricus*[11,12].

At the start point, quality of life was assessed in all probiotic and placebo patients using the Pediatric Quality of Life Inventory™ 4.0 Short form questionnaire (PedsQL™ 4.0 SF 15). Patients were followed in CF clinic every week through phone contacts and included evaluation of compliance to treatment and regularity of intake. PedsQL™ 4.0 is a valid and reliable questionnaire which is tested repeatedly in several pediatric populations[16-18]. Validity of the Farsi version was confirmed by a committee comprising methodologists, health professionals, language professionals, and psychologists. Reliability was

approved by test and re-test and finding no significant differences between answers (Intraclass Coefficient Correlation, alpha=0.89 child; 0.92 parent report)[17]. PedsQL™ questionnaire is conducted for three age groups: 2-4, 5-7, and 8-12 years of age. The first age group (2-4) has only parent-proxy version, while the second and third age groups (5-7 and 8-12) have both child and parent-proxy versions. Answers are based on patient's function in various fields such as physical, emotional, social, and educational during the past one month. There are five choices for each question, ranging from always to never. Each question is scored from 0 to 100 as follows:
First choice: "Never" scored 100,
Second choice: "Almost never" scored 75,
Third choice: "Sometimes" scored 50,
Forth choice: "Almost always" scored 25,
Fifth choice: "Always" scored 0.

The questionnaires were filled out by a trained nurse who was unaware about the principles of study. Three and six months after completing probiotic treatment period, the PedsQL™ questionnaires were again completed by the same nurse, using the same questionnaire. Quality of life score was determined totally and separately in four different fields of children's function.

Number of episodes of pulmonary exacerbation, together with number and duration of subsequent hospital admission in probiotic patients were obtained during three months after probiotic treatment and compared to the same three months of the previous year. Pulmonary exacerbation was identified based on CF Foundation criteria including an increase in pulmonary symptoms and secretions which required oral or intravenous antibiotics[19].

Statistical analysis of data performed using SPSS (11.5). t-Student test was used to compare the total and function specified scores of the quality of life between probiotic and placebo patients. Paired sample t-test and ANOVA compared the number of pulmonary exacerbation in probiotic and placebo patients during three months after intervention with the same three months of previous year. $P<0.05$ was considered statistically significant.

Findings

All patients enrolled in both groups (placebo group: 7 females, 13 males, mean age 5.36±2.66 years; placebo group: 10 females, 7 males, mean age 5.50±2.55 years) completed the study period. Baseline quality of life and demographic characteristics of patients are shown in Table 1.

Quality of life:

Baseline quality of life total scores had no significant difference among probiotic and placebo patients (t-Student test, $P=0.39$ and $P=0.72$ respectively in both child and parent reports). Scores of quality of life were compared between probiotic and placebo groups after three and six months of probiotic treatment as well, the results are displayed in Table 2 separately for each field of function. Significant difference existed in the total scores of quality of life after three months, but not after six months of intervention, based on parent report ($P=0.01$ and $P=0.17$ respectively). Children report had no significant results in the total scores after three and six months ($P=0.60$ and $P=0.85$ respectively).

Pulmonary evaluation:

There was no significant difference between patients of probiotic and placebo group in pulmonary exacerbation during one year before intervention (ANOVA, $P=0.25$). However, during and three months after intervention, significant difference developed in number of pulmonary

Table 1: Baseline quality of life and demographic characteristics of enrolled patients

Parameter		Probiotic group (n=20)	Placebo group (n=17)	*P* value
Gender (M/F)		13/7	7/10	0.2*
Mean age (year)		5.36	5.5	0.9‡
Quality of life (mean total score)	Child report	87.93 (10.57)	84.50 (7.05)	0.4‡
	Parent report	80.20 (10.41)	79.11 (7.61)	0.7‡

* Fisher's exact test ‡ t-Student test

Table 2: Comparing the scores of quality of life between probiotic and placebo patients at baseline, 3rd, and 6th month of probiotic treatment reported by *P*-value

		3 months after treatment				6 months after treatment			
		Parent report		Child report		Parent report		Child report	
		Mean (SD)	*P**	Mean (SD)	*P**	Mean (SD)	*P**	Mean (SD)	*P**
Physical	**Probiotic group**	85.2 (10.9)	0.02	88.1 (13.6)	0.07	83.0 (12.3)	0.2	84.8 (10.4)	0.1
	Control group	80.0 (11.0)		81.0 (9.9)		77.9 (11.3)		80.5 (11.6)	
Emotional	**Probiotic group**	81.5 (10.4)	0.7	84.6 (14.3)	0.1	74.0 (16.8)	0.9	84.0 (16.3)	0.1
	Control group	76.8 (8.7)		81.2 (5.8)		73.1 (12.0)		83.7 (6.0)	
Social	**Probiotic group**	87.1 (9.1)	0.7	92.6 (9.6)	0.01	83.4 (14.5)	0.03	89.7 (11.9)	0.2
	Control group	78.3 (7.0)		83.1 (6.6)		76.8 (10.5)		81.8 (6.8)	
School	**Probiotic group**	93.4 (7.7)	0.6	96.0 (7.0)	0.6	89.6 (11.8)	1.0	94.3 (7.1)	0.6
	Control group	90.8 (8.3)		95.0 (8.7)		89.3 (9.5)		95.0 (8.7)	
Total	**Probiotic group**	86.8 (6.7)	0.01	90.3 (8.1)	0.6	82.5 (10.3)	0.2	88.2 (8.4)	0.8
	Control group	81.4 (5.2)		85.9 (6.1)		79.3 (8.6)		85.2 (4.8)	

* *P* value: t-Student test (α=0.05); SD: Standard Deviation

exacerbation between patients of two groups (ANOVA, *P*=0.002 and *P*=0.0001 respectively).

During probiotic supplementation, none of patients experienced pulmonary exacerbation, requiring either intravenous or oral antibiotic treatments. Number of pulmonary exacerbations in outpatients who were orally treated with antibiotics during three months after probiotic supplementation, compared to the same three months of the previous year was statistically significant (Paired sample t-test, *P*<0.01), while no significant difference was noted in number of pulmonary exacerbations in inpatients who were intravenously treated with antibiotics (Paired sample t-test, *P*=0.96) (Table 3).

Discussion

This study indicates that probiotic supplementation containing mixed micro-organisms can improve quality of life and reduce pulmonary exacerbation in children with cystic fibrosis.

Preliminary researches based on treating non-intestinal infectious statuses of animals were the main cause of raising the assumption that probiotics may have anti-infectious effects in sites other than the gastrointestinal tract: *Lactobacillus casei* enhanced lung clearance in young mice[20] and *Lactobacillus plantarum* prevented the pathogenic activity of *P. aeruginosa* in burned-mouse model[21]. Beneficial effects of probiotic treatment are thought to be through modification of intestinal microbiota and preventing deleterious effects of inflammatory cytokines (TNF-α and IFN-γ) on epithelial function leading to a less disrupted intestinal barrier[22].

There are evidences confirming the efficacy of probiotics on several intestinal inflammatory diseases such as inflammatory bowel disease, childhood gastroenteritis, acute diarrhea and cystic fibrosis[8,23-25]. There are several mechanisms that probiotics act to reduce intestinal and non-intestinal inflammation. The effects of probiotics on immune-related diseases, common cold and type-2 diabetic patients have been reported in previous studies in Iran[7,26, 27].

Whether probiotics can prevent pulmonary deterioration in CF patients, is a concern. Bruzzese

Table 3: Number of pulmonary exacerbation (Mean ± SD) in 2 groups of cystic fibrosis patients with oral and IV antibiotic therapy, prior to and after probiotic supplementation (n=20)

	Before intervention*	During intervention	After intervention‡	*P value* Δ
Oral antibiotic treatment (outpatient)	2.05 (1.82)	0	0.7 (1.03)	0.01
IV antibiotic treatment (inpatient)	0.2 (0.52)	0	0	0.1

* During the same three months of the previous year ; ‡ During three months after completing treatment period
Δ Paired sample t-test

et al[12] investigated the impact of *Lactobacillus GG* on pulmonary exacerbation through a placebo-controlled, prospective pilot study, and indicated a significant decrease in pulmonary exacerbation and hospital admission for intravenous antibiotic therapy as well as improvement in FEV_1 and BMI in CF patients. Four years later, Weiss et al[11] operated a prospective pilot study resulting in reduction of pulmonary exacerbation, but no changes in pulmonary function tests (PFTs). What we attained was significant decrease in number of pulmonary exacerbations which were orally treated with antibiotics (in outpatients), not the intravenously treated ones (in inpatients). This insignificancy in admission rate in comparison with Bruzzese findings may be due to short period of probiotic supplementation. More reliable judge on relationship between probiotic treatment and number of admissions in CF patients might be achieved through longer treatment and follow-up periods.

Assessing the quality of life in chronic illnesses such as cystic fibrosis has increasingly been introduced as an important appendix to medical outcome parameters in evaluating disease progression[28]. It is considered that better lung function, directly improves nutritional status[29] and consequently, a good nutrition results in an improved quality of life[15]. Different pulmonary rehabilitation programs and nutritional supplementations are suggested to improve pulmonary function and quality of life in CF patients[14]. Prior studies which have evaluated the effects of probiotics on quality of life in CF patients are rather limited. This study showed a significant improvement in quality of life of the probiotic patients compared with placebo patients three months after completing probiotic treatment, but there was no significance after 6th month. This indicates that probiotic supplementation might have temporary effects on quality of life and the ingestion should be continued for steady effects.

An increase in total score of quality of life only existed in parent report and not the child one and was exclusively related to physical functioning according to *P*-values of other fields of function. This indicates that the probiotic used in this study has higher improving effect on physical functioning of CF patients rather than social, emotional, and educational functioning. This varying effect of probiotics on different aspects of life quality might be due to faster effect of better pulmonary function on physical aspect in CF patients. Social, emotional and educational functioning might need a longer period of time to indicate significant improvement.

Most of our patients in both groups were too young (Mean age of 5.43 years), Therefore, it was difficult to evaluate pulmonary function by PFTs and resulted in absence of baseline information about the severity of lung disease. Moreover, it is recommended to assess the fecal colonization of micro-organisms after probiotic treatment which was not performed in current study.

Previously, we had indicated that quality of life in CF patients are significantly lower in all four aspects of children functioning in comparison with normal pediatric population[30], current study concluded that probiotics might be useful nutritional supplements for reducing the number of pulmonary exacerbation and improving the quality of life in CF patients. Effects of this product on quality of life seem to be temporary and continuous ingestion is needed for much more stable effects. Further prospective, placebo-controlled studies applying more patients and longer treatment and follow-up periods are recommended to better evaluate the value of probiotics on reducing pulmonary deterioration and quality of life in patients with cystic fibrosis.

Acknowledgment

The authors want to appreciate the Research Chancellor of Mashhad University of Medical Sciences for financial support. They also thank Dr. Hossein Bagheri and Dr. Ramin Sadeghi for editing the manuscript and Dr. Monavar Afzalaghaee for statistical analysis. The results described in this paper were part of student thesis (proposal number: 88660). Trial Registration no.: IRCT20120527982.

Conflict of Interest: None

References

1. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* 2003;168(8): 918-51.

2. van Elburg RM, Uil JJ, van Aalderen WMC, et al. Intestinal permeability in exocrine pancreatic insufficiency due to cystic fibrosis or chronic pancreatitis. *Pediatr Res* 1996;39(6):985-91.
3. Claeys S, van Hoecke H, Holtappels G, et al. Nasal polyps in patients with and without cystic fibrosis: a differentiation by innate markers and inflammatory mediators. *Clin Exp Allergy* 2005;35(4):467-72.
4. Bruzzese E, Raia V, Gaudiello G, et al. Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. *Aliment Pharmacol Ther* 2004;20(7):813-9.
5. Infante Pina D, Redecillas Ferreiro S, Torrent Vernetta A, et al. Improvement of intestinal function in cystic fibrosis patients using probiotics. *Ann Pediatr (Barc)* 2008;69(6):501-5.
6. Young RJ, Huffman S. Probiotic use in children. *J Pediatr Health Care* 2003;17(6):277-83.
7. Homayouni Rad A, Torab R, Ghalibaf M, et al. Might patients with immune-related diseases benefit from probiotics? *Nutrition* 2013;29(3):583-6.
8. Allen SJ, Okoko B, Martinez E, et al. Probiotics for treating infectious diarrhoea. Cochrane Database Syst Rev 2004(2):CD003048.
9. Kalliomaki M, Salminen S, Poussa T, et al. Probiotics and prevention of atopic disease: 4-years follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361(9372):1869-71.
10. Khodada A, Farahmand F, Mehri N, et al. Probiotics for the treatment of pediatric helicobacter pylori infection: a randomized double blind clinical trial. *Iran J Pediatr* 2013;23(1):79-84.
11. Weiss B, Bujanover Y, Yahav Y, et al. Probiotic supplementation affects pulmonary exacerbations in patients with cystic fibrosis: a pilot study. *Pediatr Pulmonol* 2010;45(6):536-40.
12. Bruzzese E, Raia V, Spagnuolo MI, et al. Effect of Lactobacillus GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: A pilot study. *Clin Nutr* 2007;26(3):322-8.
13. Perdigon G, Fuller R, Raya R. Lactic acid bacteria and their effect on the immune system. *Curr Issues Interest Microbiol* 2001;2(1):27-42.
14. Schmitz TG, Goldbeck L. The effect of inpatient rehabilitation programmes on quality of life in patients with cystic fibrosis: A multi-center study. *Health Qual Life Outcomes* 2006;4:8.
15. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med* 2011;183(11):1463-71.
16. Varni JW, Burwinkle TM, Seid M. The PedsQL™ as a pediatric patient-reported outcome: Reliability and validity of the PedsQL™ Measurement Model in 25,000 children. *Expert Rev Pharmacoecon Outcomes Res* 2005;5(6):705-19.
17. Varni JW, Burwinkle TM, Seid M. The PedsQL™ 4.0 as a school population health measure: Feasibility, reliability, and validity. *Qual Life Res* 2006;15(2): 203-15.
18. Bastiaansen D, Koot HM, Bongers IL, et al. Measuring quality of life in children referred for psychiatric problems: Psychometric properties of the PedsQL™ 4.0 Generic Core Scales. *Qual Life Res* 2004;13(2): 489-95.
19. Follow guidelines in Cystic Fibrosis Foundation. Mycrobiology and infectious disease in Cystic Fibrosis. Consensus Conferences: Concept in care. Bethesda, 1994,Vol V, sect 1.
20. Alverez S, Herrero C, Bru E, et al. Effect of Lactobacillus casei and yogurt administration on prevention of Pseudomonas aeruginosa infection in young mice. *J Food Prot* 2001;64(11):1768-74.
21. Valdez JC, Peral MC, Rachid M, et al. Interference of Lactobacillus plantarum with Pseudomonas aeruginosa in vitro and in infected burns: the potential use of probiotics in wound treatment. *Clin Microbiol Infect* 2005;11(6):472-9.
22. Resta-Lenert S, Barrett KE. Probiotics and commensals reverse TNF-alpha- and IFN-gamma-induced dysfunction in human intestinal epithelial cells. *Gastroenterology* 2006;130(3):731-46.
23. Neil FR, Albert DL. Probiotics in the treatment of human inflammatory bowel diseases: update 2008. *J Clin Gastroenterol* 2008;42 (Suppl 2):S97-103.
24. Heydarian F, Kianifar HR, Ahanchian H, et al. A comparison between traditional yogurt and probiotic yogurt in non-inflammatory acute gastroenteritis. *Saudi Med J* 2010;31(3):280-3.
25. Kianifar HR, Farid R, Ahanchian H, et al. Probiotics in the treatment of acute diarrhea in young children. *Iran J Med Sci* 2009;34(3):204-7.
26. Homayouni Rad A, Torab R, Mortazavian AM, et al. Can probiotics prevent or improve common cold and influenza? *Nutrition* 2013; 29(5):805-6.
27. Ejtehad HS, Mohtadi-Nia J, Homayouni-Rad A, et al. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. *Nutrition* 2012; 28(5):539-43.
28. Bruzzese E, Raia V, Spagnuolo MI, et al. Effect of Lactobacillus GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: a pilot study. *Clin Nutr* 2007; 26(3):322-8.
29. Corey M, McLaughlin FJ, Williams M, et al. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;41(6):583-91.
30. Kianifar HR, Bakhshoodeh B, Hebrani P, et al. Qulaity of life in cystic fibrosis children. *Iran J Pediatr* 2013;23(2):149-53.