Research Square

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Does synbiotic supplementation affect the quality of life in children with cystic fibrosis? A pilot randomized controlled clinical trial

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Research article

Keywords: quality of life, cystic fibrosis, synbiotic, children

Posted Date: July 15th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-23845/v2

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Version of Record: A version of this preprint was published on October 15th, 2020. See the published version at https://doi.org/10.1186/s40795-020-00373-4.

Abstract

Background: There is no clinical trial that assesses the effect synbiotic supplementation on HRQOL in CF children. Considering the importance of HRQOL as an essential primary outcome and determinant of therapeutic benefit in chronic diseases like cystic fibrosis, the present clinical trial aimed to determine the efficacy of synbiotic supplementation on HRQOL in children with CF.

Methods: In the present double-blind randomized clinical trial, 40 CF children were randomly allocated to the two groups. The intervention group was supplemented with synbiotics supplements and the patients in the placebo group received maltodextrin for six months. Demographic data and information about antibiotic use were recorded using the questionnaire. The health-related quality of life was assessed using the Persian version of quality of life inventory questionnaires. Paired t-test and ANCOVA were used for statistical analysis.

Results: Totally, 36 participants completed the trial. The mean score of HRQOL was 76.34±17.33. There were no significant differences between synbiotic and placebo groups regarding baseline demographic and quality of life characteristics. Compared with baseline values, the mean total score and subscores of quality of life did not change significantly after synbiotic and placebo supplementation ($p>0.05$). Moreover, the results of ANCOVA showed that there were no significant differences between the two groups regarding the post-trial value of HRQOL total score and subscores.

Conclusion: According to results, six-month supplementation with synbiotic did not have a significant effect on the HEQOL in children with CF. However, further studies with larger sample sizes and using more disease-specific questionnaires are needed for a more precise conclusion.

The protocol of the study was registered at Iranian registry clinical trials (Registration code: IRCT2017011732004N1; Registration date: 2017-02-14).

Background:

Cystic fibrosis (CF) is a multi-organ and life-limiting disease [1] that is associated with respiratory infections and gastrointestinal inflammation with a possible association with intestinal dysbiosis [2, 3]. According to earlier reports, treatment interventions, special dietary regimen, and also intestinal dysfunction usually resulted in gastrointestinal dysbiosis in CF children that may contribute to different complications [4]. Considering the effect of probiotic bacteria on pathogen bacteria, different studies were conducted to assess the effect of probiotics supplementation in CF patients and some of them reported promising results [5-9]. However, only limited data is available about the effect of this supplement on health-related quality of life (HRQOL) in CF children. The only previous study that examined the effect of one-month supplementation of probiotics (2×10^9CFU/d) on quality of life in CF children showed that there was no significant difference between intervention and placebo groups regarding children report of HRQOL. However, the parents' report indicated significant improvement in the physical and total score of quality of life [10]. Supplementation duration in this study was limited and it

seems that a study with longer treatment duration would be of value. On the other hand, previous studies showed that synbiotic supplements (have both prebiotic and probiotic properties) may have a synergistic effect on the intestinal microbiota [11, 12]. However, there is no clinical trial that assesses the effect synbiotic supplementation on HRQOL in CF children. Considering the importance of HRQOL as an essential primary outcome and determinant of therapeutic benefit in chronic diseases like cystic fibrosis, the present clinical trial aimed to determine the efficacy of synbiotic supplementation on HRQOL in children with CF.

Methods:

In the present double-blind randomized placebo-controlled clinical trial, the CF patients were selected from Tabriz Children's Hospital affiliated with Tabriz University of medical sciences. The diagnosis of CF was confirmed by a pediatrician according to clinical signs and two sweat chloride test (> 60 mmol/L). The children were included if they aged 5-12 years with Tiffeneau-Pinelli index>40% and the absence of recent acute exacerbation. The exclusion criteria were: having other related diseases such as liver or endocrine diseases, having ventilator-dependent respiratory failure, or had regular use of probiotics and probiotic fortified food were excluded from the study. Forty children with CF met inclusion/exclusion criteria and entered the study.

Written informed consent was obtained from all children's parents. This study was approved by The Ethics Committee of Tabriz University of Medical Sciences) IR.TBZMED.REC.1395.919). The protocol was registered at Iranian registry clinical trials (IRCT2017011732004N1).

Experimental design

Forty patients were randomly divided into intervention and placebo groups according to their age and sex. The randomization was done using a computer-generated random table by a researcher who was not involved in the other part of this research. Patients and the assessor were blind to treatment allocation.

The sample size was calculated based on Whitehead study [13] that recommended 15 samples per arm in pilot clinical trials with considering 90% power, two-sided 5% significance, medium effect size (0.5).

The patients in the intervention and placebo groups were instructed to consume two synbiotic or maltodextrin capsules per day for six months. The synbiotic supplement was purchased from Zist Takhmir company and it contains *Lactobacillus casei* (3.5×10^9 CFU/g), *Lactobacillus acidophilus* (1×10^9 CFU/g), *Lactobacillus rhamnosus* (7.5×10^8 CFU/g), *Lactobacillus bulgaricus* ($10^8 \times$ CFU/g), *Streptococcus thermophilus* (1×10^8 CFU/g), *Bifidobacterium breve* (1×10^{10} CFU/g), *Bifidobacterium longum* (3.5×10^9 CFU/g) and 38.5 mg *Fructo-oligosaccharides as prebiotic* [14]. The patients were asked to take capsules at least 2 hours apart from antibiotics. Patients were instructed to return the unused capsules. The patients who did not adhere to study protocol (consume less than 80% of prescribed supplements) or changed their medicines were excluded.

Outcome measures:

In this clinical trial, different outcomes including anthropometric measurements, hospitalization duration, antibiotic use, clinical outcomes, and quality of life were studied. All outcomes except the quality of life outcomes were reported in our previous study [14]. In the present study, we reported the effect of synbiotic supplementation on HRQOL in children with CF.

The health-related quality of life was assessed using the Persian version of quality of life inventory questionnaires (PedsQL). The validity of the Iranian version of this questionnaire was investigated previously [15]. The questionnaires had 23 items on a five-point Likert scale ranging from 0 (never a problem) to 4 (almost always a problem). According to the questionnaire instruction [16], the scores were transformed on a scale from 0 (score 4) to 100 (score 0) and the total score and dimensions scores were calculated by summing of the items over the number of items answered. The questionnaire includes the following dimension scores: physical (8 questions), emotional (5 questions), social (5 questions), and school functioning (5 questions). The final HRQoL total score and dimension scores were computed out of 100. A change of 4.5 in the PedsQL summary score was considered as the minimal clinically important difference (MCID) [17]. The questionnaire was completed before and six months after supplementation

Statistical analysis

All analyses were conducted using SPSS 22.0 and based on intention to treat (ITT) analysis. The Kolmogorov-Smirnov test was used for checking the normality. The within-group comparisons were performed by paired sample t-test. The between-group analysis was done using independent sample t-test and chi-square tests. One way ANCOVA was used to compare the quality of life score after intervention by adjusting to the baseline values. The significance level was considered P-value ≤ 0.05.

Results:

Figure 1 shows the patients` recruitment, and analysis diagram. According to the figure, thirty-six participants completed the trial. The patient's mean age was 8.72±3.23 years. About 52% of them were male. The mean Forced expiratory value in one second (FEV_1) (%) was 82.00±28.49 and 79.42±23.62 in synbiotic and placebo groups respectively. The mean score of quality of life was 81.10±16.81. There were no significant differences between synbiotic and placebo groups regarding baseline demographic and quality of life characteristics.

Table 2 presents the mean total score and subscores of quality of life in synbiotic and placebo groups. As can be seen, compared with baseline values, the mean total score and subscores of quality of life did not change significantly after probiotic and placebo supplementation ($p>0.05$). Moreover, the results of ANCOVA also showed that there were no significant differences between the two groups regarding the post-trial value of quality of life total score and subscores. Moreover, the changes were not clinically meaningful.

Discussion:

Considering the association of CF with intestinal dysbiosis, in the present study, we studied the effect of synbiotic supplementation on HRQOL in children with CF. HRQOL is an important and essential primary outcome and determinant of therapeutic benefit in chronic diseases such as cystic fibrosis. Previously, different studies have assessed the effect of probiotic supplementation on other childhood respiratory and gastrointestinal diseases and providing conflicting results. For example, Huang et al showed that the probiotic supplementation did not significantly affect the QOL in children with asthma [18]. However, Guandalini, et al showed the promising effect of the probiotic mixture on QOL in children with irritable bowel syndrome [19].

In the present study, we showed that compared with placebo, synbiotic supplementation did not have a significant effect on the quality of life in these patients. In addition, considering the MCID of 4.5, the differences were not clinically important. To the best of our knowledge, only limited data is available regarding the effect of probiotic supplementation on quality of life in these patients. In line with the results of the present study, Jaffari et al also showed no significant difference between intervention and placebo groups regarding children's reports of health-related quality of life. However, the parents' report indicated significant improvement in the physical and total score of quality of life [10]. In the present study, we did not assess the parents' report of child HRQOL. The observed effect of probiotic supplementation on parents' reports of HRQOL in the mentioned study may be attributed to the differences in disease severity. Although Jaffari et al, did not report the FEV1, none of their patients received antibiotics during the intervention period. However, in the present study, 35.3% and 55% of patients in the intervention and placebo groups (p=0.32) respectively received antibiotics during the study [14]; this may be due to a longer duration of supplementation or higher severity of diseases in the present study.

The observed lack of significant effect of synbiotic supplementation on HRQOL in CF children in the present study may be partly due to the lack of its effect on pulmonary exacerbation [14]. Some studies reported the positive effect of probiotic supplementation on pulmonary and intestinal manifestations. So, we postulated that through this mechanism, synbiotic may improve HRQOL in CF children. However, we showed that this supplement did not reduce pulmonary exacerbation [14] and nor did HRQOL in CF patients

The results of the present study should be interpreted according to the following limitations. We did not consider the parental report of quality of life. Moreover, the sample size was limited and we did not use the CF specific quality of life assessment questionnaire. Moreover, we did not have a follow-up period to assess the long term effect of synbiotic supplementation on quality of life. However, the duration of supplementation in the present study seems to be long enough to assess changes in quality of life.

Conclusion:

Briefly, According to the results, six-month supplementation with synbiotic did not have a significant effect on the quality of life total score and subscores in children with CF. To the best of our knowledge, this is the first study that assesses the effect of synbiotic in these patients and the data regarding the effect probiotic supplements on quality of life in these patients are also scarce. So, further studies with larger sample sizes and using more disease-specific questionnaires are needed for a more precise conclusion.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all children's parents. This study was approved by The Ethics Committee of Tabriz University of Medical Sciences) IR.TBZMED.REC.1395.919)

Availability of data and materials

The dataset supporting the conclusions of this article is included in the article.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

Funding

This study was funded by the Liver and gastrointestinal diseases research center, Tabriz University of medical sciences, Tabriz, Iran. The funder had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

ZN, LN, and NB were responsible for the conception and design of the study. LN and EM were responsible for data acquisition. LN and MAF were responsible for data analysis. ZN, LN, EM, and NB were responsible for data interpretation. EM and ZN drafted the manuscript; all other authors revised and commented on the draft. All authors read and approved the final version of the manuscript.

Acknowledgments

The authors thank the East Azerbaijan CF patients who participated in the study.

Abbreviations

ANCOVA: One-way Analysis of Covariance (ANCOVA) CF: Cystic fibrosis FEV1: Forced expiratory value in one score HRQOL: Health-related quality of life

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Tables

Table 1

Baseline characteristics of participants.

Variables	Synbiotic (n = 20)	Placebo (n = 20)	p-value*
Age (years)	8.29 ± 2.11	9.25 ± 3.99	0.35
Sex (M/F)	9/11	12/8	0.26**
FEV1 (%)	81.75 ± 27.51	80.29 ± 22.84	0.68
Quality of life (total score)	72.76 ± 17.96	79.92 ± 16.42	0.23
Physical score	67.64 ± 22.93	73.71 ± 19.48	0.41
Emotional score	66.47 ± 22.62	79.41 ± 22.63	0.10
Social score	79.41 ± 22.21	82.05 ± 10.61	0.66
School performance score	80.58 ± 19.43	88.23 ± 18.70	0.25
M: Male; F: Female; FEV: Forced Expiratory Volume			
*p-value of independent t-test			
**p-value of chi-square			

Table 2

Comparison of the quality of life score and subscores between two groups

Variables		Synbiotic (n = 20)	Placebo (n = 20)	p-value
Quality of life (total score)	Before	72.76 ± 17.96	79.92 ± 16.42	0.23**
	After	73.52 ± 16.74	79.95 ± 15.57	0.95¥
	p-value*	0.08	0.69	
Physical score	Before	67.64 ± 22.93	73.71 ± 19.48	0.41**
	After	69.30 ± 20.40	74.26 ± 18.37	0.58¥
	p-value*	0.07	0.48	
Emotional score	Before	66.47 ± 22.62	79.41 ± 22.63	0.10**
	After	66.17 ± 21.39	79.37 ± 21.28	0.74¥
	p-value*	0.57	0.61	
Social score	Before	79.41 ± 22.21	82.05 ± 10.60	0.66**
	After	80.00 ± 20.76	82.04 ± 9.69	0.75¥
	p-value*	0.33	0.91	
School performance score	Before	80.58 ± 19.43	88.23 ± 18.70	0.25**
	After	81.17 ± 19.08	89.11 ± 18.64	0.69¥
	p-value*	0.33	0.45	

*p-value of paired sample t-test

**p-value of independent sample t-test

¥ p-value of ANCOVA after adjusting for baseline values

Figures

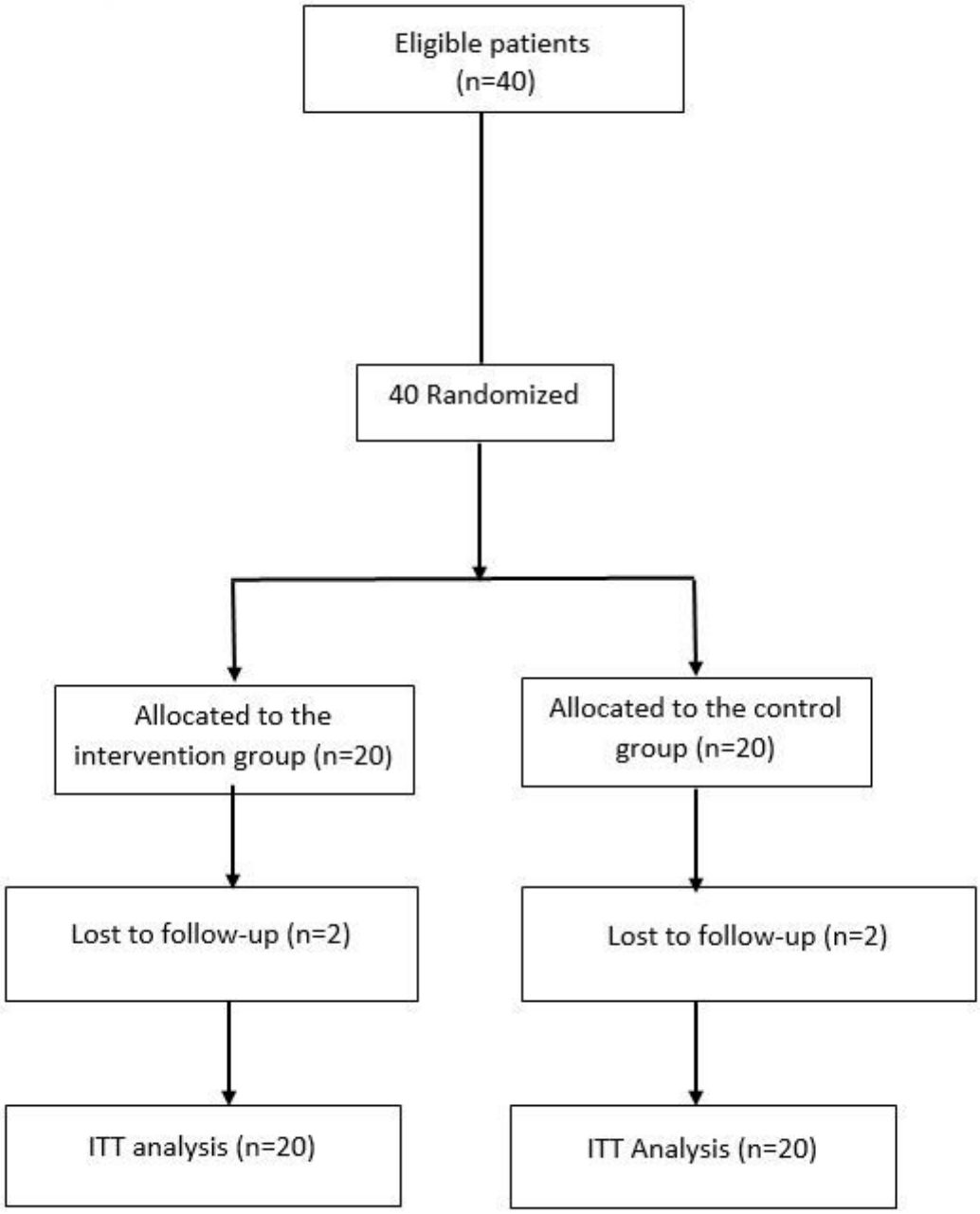

Figure 1

Flow chart of patients' recruitment and analysis

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- CONSORT2010Checklist.doc