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Efficacy of Saccharomyces Boulardii in Pediatrics with Functional Abdominal Pain: A Randomized Controlled Trial

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Abstract

Background: Considerable increase in gut motility after probiotic supplementation consumption is indicated in recent studies. The present study conducted to clarify whether supplementation with Saccharomyces boulardii can palliate the abdominal pain frequency in children with Functional Abdominal Pain (FAP).

Methods: The present clinical trial was conducted on children referred to the Pediatric Departments of the Imam Khomeini hospital, Ilam, Iran, and Shahid Beheshti Hospital, Kashan, Iran. The patients were randomized to receive either 250 mg oral supplementation of Saccharomyces boulardii, Zist Takhmir Company, or placebo, twice daily for 3 weeks before the first clinical assessment. The intensity of the symptoms were evaluated using the OUCHER PAIN scale.

Results: A total of 104 FAP children with a mean age of 9.51±3.52 years enrolled in the study. 52 of them were randomly assigned to the treatment group and 52 patients were assigned to the placebo group. Statistical analyses demonstrated that the treatment with Saccharomyces boulardii was effective after the 1st week of the study. (P-value=0.001)

Conclusion: To the best of our knowledge, our investigation is the first trial, assessing the correlation between taking Saccharomyces boulardii and symptom reduction in FAP children through its probiotic effects. This disorder can be considered as a multifactorial disease, which further investigations are needed to figure out its risk factors and treatment modalities.

Key Words: Functional Abdominal Pain, Pediatrics, Randomized controlled trial, Saccharomyces boulardii,.

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1- INTRODUCTION

Saccharomyces boulardii is a non-pathogenic yeast generally used in a lyophilized formula in many countries of the world. Children and adults are two candidates for its therapeutic prescription. Efficient application of Saccharomyces boulardii in either prevention or treatment of several gastrointestinal disorders has been proven in some clinical trials. (1-4)

Clinical and pharmacological findings imply that Saccharomyces boulardii, which is not considered as a probiotic food, is a bio-therapeutic agent that improves the physiological function of the digestive tract. Probiotic foods, that are used to fortify milk or yoghurt, include another sort of microorganisms or nutrients that can change the gastrointestinal microflora (5).

Functional Abdominal Pain (FAP) presents with recurrent abdominal pain and is one the most common disorders which afflicts roughly 20% of all school-aged children beside its minor dominance in older than 9 years of age girls (6). Formerly, FAP was known as a pain syndrome which was defined as at least 3 episodes of abdominal pain that takes more than 3 months. The pain acuity and intensity may disrupt daily activities (7).

Administrating sufficient amounts of probiotics may gain beneficial health related outcomes. A remarkable measure to the treatment of chronic abdominal pain could be defined by using Saccharomyces boulardii as a bio-therapeutic agent, which basically takes action through the regulation of the gut microbial flora (8). Anti-pathogen effects, encountering with gastrointestinal path and self-protection by colonizing through the tract, (9, 10) and incorporation with CD4 T-helper cells which fire up the cytokines release, are the explanations of how it can affects the tissue on the distal part of the intestine, literally (10).

Moreover, amelioration of the gut motility through supplementation with these probiotics is argued in recent studies (10). Our study aimed to determine whether supplementation with Saccharomyces boulardii could lead to decrease and perseverance of recurrent abdominal pain in children with FAP.

2- MATERIALS AND METHODS

2-1. STUDY DESIGN

The aim was to investigate the effect of Saccharomyces boulardii supplementation on the intensity of FAP in children. The present clinical trial was conducted on patients recruited from children referred to the Pediatric Departments of the Imam Khomeini hospital, Ilam, Iran, and Shahid Beheshti Hospital, Kashan, Iran. The procedure was approved by the Ethics Committee of Ilam University of Medical Sciences, Ilam, Iran. (Ethic code: 110.1396.rec.medilam.ir) and this clinical trial was registered with ID: IRCT20180822040850N1.

Participants

Potentially qualified patients were screened using a diary to register symptoms, the intensity of daily pain, and any symptoms 3 weeks prior to involvement. Using this diary, patients between 5 and 15 years of age with FAP as defined in the Rome IV criteria (11) were enrolled. According to the specific Rome IV criteria for inclusion, we defined FAP as chronic or recurrent gastrointestinal symptoms not described by structural or biochemical abnormalities (12).

All parents were comprehensively informed about the goals of the study, and informed consent was obtained from at least one parent prior to inclusion. Exclusion criteria were organic disorders (established by medical history, urine analysis, complete blood count, stool examination for occult blood and parasites, abdominal ultrasound and screening for

celiac disease), other chronic diseases and history of growth failure.

2-2. PROCEDURES AND OUTCOMES

At first 115 patients were recruited in the study. 6 patients excluded due to the abnormal laboratory findings and 4 patients excluded due to unwillingness to continue the study. Also, one patient was excluded due to positive risk factors. Finally, 104 patients were randomized to receive either 250 mg oral supplementation with Saccharomyces boulardii (Zist Takhmir Company) (n = 52) or placebo with similar appearance to the manufactured drug (n = 52), twice daily for 3 weeks before the first clinical assessment. Randomization was based on a computer-generated list, which was retained by a pharmacist at each center to ensure allocation concealment. Supplementation was stopped after 3 weeks, and the patients followed up after further 3 weeks.

The patients used a diary to record intensity of pain and any other symptoms. The symptoms diary was reserved daily by the parents and reported information on the intensity of pain periods, location of pain, presence or absence of associated symptoms and interfering with normal activities. The intensity of the symptoms were evaluated by using the OUCHER PAIN scale based on educated parent's reports (13). The adherence to the treatment was monitored in the diary. The outcomes were defined as the reduction of the intensity of FAP.

Both the Saccharomyces boulardii supplementation and placebo study products were manufactured by Biotechnology and medical plants research center, Ilam University of medical science, Ilam, Iran. The study products were preserved and refrigerated at all times to confirm the full viable count of the product during the study. The bottles were coded and blinded for the individuals and for the physicians until the study was completed and the data collected.

Statistical Analysis

All statistical analyses were done by means of SPSS version 20 software. Categorical data were compared by applying chi-square test, and continuous variables, by using t-test. Comparison of many parameters between different intervals and the baseline were performed by means of paired sample t-test. Analysis of variance tests was used when parameters of more than 2 groups were compared. Statistical significance was defined as P-value < 0.05.

3- RESULTS

A total of 104 FAP children with the mean age of 9.51±3.52 years were enrolled in the study. 52 of them were randomly assigned into the treatment group and 52 patients were assigned to the placebo group. Demographic features of the patients are reported in **Table1**. There was no significant difference between treatment and placebo groups regarding age and sex. (P-value= 0.85 and 0.84, respectively) In both groups, patients were divided into two groups regarding their ages, including 5-10-year-old patients and 10-15-year-old patients.

Table-1: Demographic features of the enrolled patients

	Treatment group (n=52)	Placebo group (n=52)
Age (mean±std)	9.4±3.23	9.55±3.34
Sex (%)	Girl (51.9 %%) Boy (48.1 %%)	Girl (57.6%) Boy (42.4%)

Average pain scores during the weeks of the study are reported in **Table 2**. In comparison, there were no significant differences between the pain scores of the patient's subgroups according to age before and after the treatment. Using ANOVA, pain score was compared between the two groups of the study. Effect of treatment with Saccharomyces boulardii on FAP was not different regarding the age of patients. (P-value=0.928) (**Fig. 2**)

Table-2: Pain scores of the studied groups during the follow-up period

	Treatment group (n=52)	Placebo group (n=52)	P-value
1st week (mean±std)	66.85±32.99	75.44±27.69	0.153
2nd week (mean±std)	35.98±28.44	47.83±10.17	0.006
3rd week (mean±std)	30.38±24.15	37.79±18.44	0.008
4th week (mean±std)	24.17±14.38	37.96±7.92	0.001
5th week (mean±std)	19.29±9.23	39.52±31.78	0.001
6th week (mean±std)	23.08±12.70	37.96±8.94	0.001

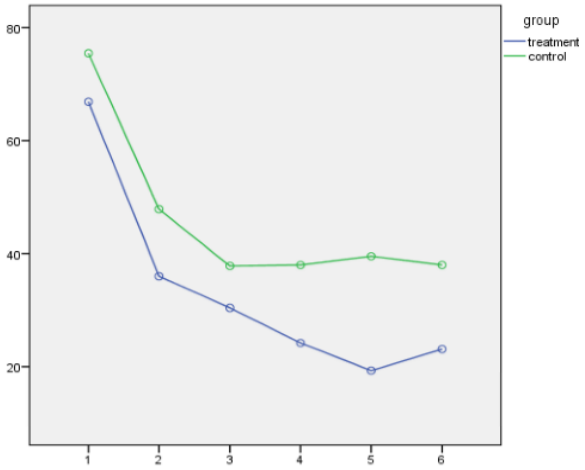

Fig. 1: Pain scores of the treatment and placebo groups during the study

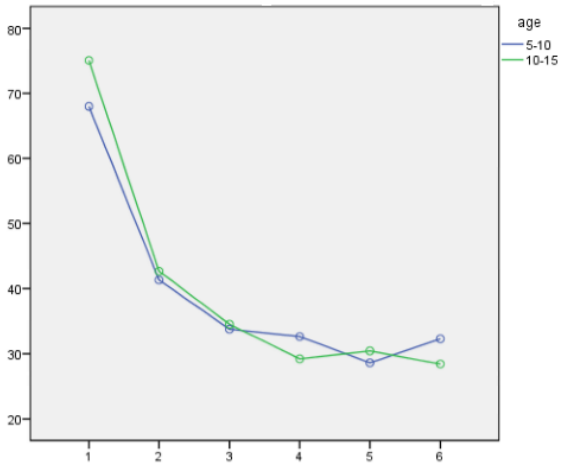

Fig. 2: Pain scores of the treatment and placebo groups regarding the age of the patients

Within the 6-week-follow up, the pain score was higher in girls; however, there was no statistically significant difference between the pain scores regarding their sex. (P-value=0.437) (**Fig. 3**)

Statistical analysis demonstrated that the treatment with Saccharomyces boulardii was effective in the treatment group after the 1st week of study. (P-value=0.001) (**Table 2**) As demonstrated in **Fig. 1**, the highest rate of declining pain was observed in the second week of study. Moreover, the minimum rate of the pain was observed in the fifth week of follow-up. The interaction effect of the treatment on the pain scores of the patients with FAP was significant. (P-value=0.048)

4- DISCUSSION

Functional abdominal pain is characteristically defined as a disorder which commonly affects children, and is recognized as a functional based complication (14). The persistence of its

complication after roughly a decade of follow-up wouldn't be out of mind (15). Probiotics are live microorganisms that if prescribed in sufficient amounts, can confer a valuable fitness consequence on FAP (8). Taking a combination of both types of probiotics, as studied in several observations, is expected to have a higher efficacy due to the interplay between yeast and bacterial probiotics which arouse their growth and extend their survival, surprisingly (16, 17).

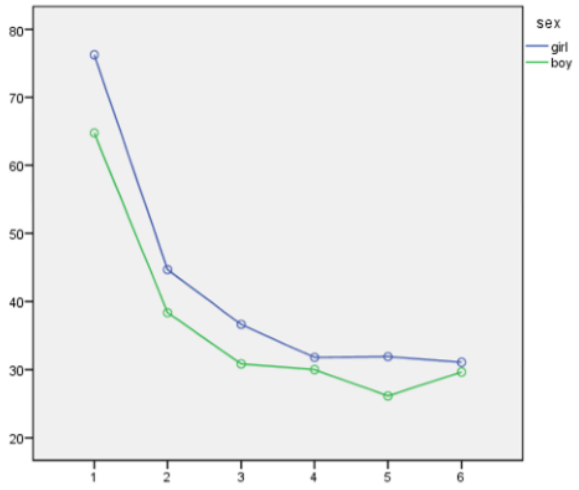

Fig. 3: Pain scores of the treatment and placebo groups regarding the sex of the patients

Several clinical trials and experimental studies strongly confirm an important role for Saccharomyces boulardii as a biotherapeutic mediator for the prevention and management of several gastrointestinal disorders; and it simplifies responses resembling the protective effects of the normal healthy gut flora (18). Saccharomyces boulardii exerts several positive influences on the patient GI tract including protective effects. It quickly reaches high concentrations in the gastrointestinal tract and remains in a viable form throughout the bowel (19) and leads to several beneficial effects on the patients' gastrointestinal tract. In a double-blind trial of S. boulardii versus placebo in the treatment of IBS patients in 2011, this probiotic agent significantly improved the quality of life, however, it did not improve intestinal symptoms (20).

We presented that there was no difference between treatment and placebo groups regarding age and sex. We also demonstrated that treatment with Saccharomyces boulardii was effective in the group after the 1st week of the study. A placebo-controlled study on 130 children aged from 3 months to 3 years, demonstrated that administration of Saccharomyces boulardii at 300 mg/d significantly decreased the frequency of abdominal pains after 48 hours of treatment (21). A systematic review and meta-analysis in 2017 on children 4-18 years of age with FAP did not reveal a significant relation between age at enrollment and placebo response (22). A randomized double-blind, placebo-controlled trial on 101 children, aged 6-15 years showed that in probiotics, Lactobacillus reuteri compared with placebo, significantly decreased the frequency and intensity of FAP in children (23). L.E. Ockeloen et al, studied 91 children, aged 1 to 18 years, with chronic abdominal pain. This study revealed that abdominal pain improved after taking lactose-restricted probiotics for five months. This improvement was similarly observed in 50% of the children after 15 months (24).

Within the 6 weeks of follow up, we demonstrated that the pain score was higher in girls, however, there was no difference between the pain scores regarding their sex. A systematic review and meta-analysis in 2017 on children 4-18 years of age with FAP revealed that the responses on Faces Pain Scales were better in the studies conducted in the Middle East, in the studies that did not report the randomization method, and in investigations with a greater percentage of women (22). A meta-analysis of 20

randomized controlled trials including 1404 patients, found a pooled relative risk for improvement in global IBS symptoms by treatments with 14 different probiotics (25).

Our investigation is the first study that evaluated the association between the consumption of Saccharomyces boulardii and its probiotic effects on symptoms of children with FAP. The low number of patients and outcome measurements were the limitations of this study. This disorder can be considered as a multifactorial disease that its risk factors and treatment modalities need further investigations.

5- CONCLUSION

To the best of our knowledge, our investigation is the first trial, assessing a correlation between taking Saccharomyces boulardii and symptom reduction in FAP children through its probiotic effects. This disorder can be considered as a multifactorial disease which further investigations are needed to figure out its risk factors and treatment modalities.

6- ETHICAL AND LEGAL CONSIDERATIONS

The procedure was approved by the Ethics Committee of Ilam University of Medical Sciences, Isfahan, Iran. (Ethic code: 110.1396.rec.medilam.ir)

7- CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

8- FUNDING

The study had no funding resources.

9- AUTHORS' CONTRIBUTION

All authors had Substantial contributions to the conception or design of the work, analysis, interpretation of data and made the final approval of the version to be published.

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