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Combination of Lactobacillus Rhamnosus LGG, Vitamin D3 and Zn in Preventing Atopic Dermatitis in Infancy

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Abstract: Introduction: With the prevalence of between 10-20% atopic dermatitis (AD) is one of the most common chronic diseases in infants and children. AD is characterized by itching and recurrent lesion. Mixtures of probiotics, including at the first place Lactobacillus rhamnosus LGG strain strains significantly decreased the risk of AD if given pre- and postnatally. Objective: The aim of the current study was to assess the effect of oral supplementation with LGG in infancy on eczema development and sensitization during the first 2 years of life. Material and methods: The study was a real life controlled observational study that included 96 patients (52 infants were treated with Lactobacillus rhamnosus with vitamin D3 and zinc, while the rest were advised to use only symptomatic treatment). Results: At the baseline the infants in the experiment group had higher values for SCORAD. During the follow up period a significant reduction in SCORAD was observed only in the group of participants who was treated with probiotics. They used also less topical treatments and antihistamines. Conclusions: This study has found that Lactobacillus rhamnosus GG (LGG) formulation with Zn and vitamin D3 supplementation during the postnatal period (in infancy and early childhood) reduce the severity of atopic dermatitis. Based on the findings it is recommended to introduce probiotic supplementation as well as vitamin D3 and zinc in infants and children with atopic dermatitis and positive family history.

Keywords: Atopic Dermatitis, Infants, Probiotics

1. Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disorders that affects around 20% of children. [1] It is considered as a very initial manifestation of the atopic march. In that context of atopic march atopic dermatitis may precede allergic rhinitis and/or asthma. It is of a great importance to identify those infants at high risk to develop allergies at early stage in order to tailor prevention and disease-modifying strategies. About 30% of children who developed the disease in the first weeks or months of life (early onset) will suffer from some kind of respiratory allergies later in life. Another half will have manifestation of AD before puberty. [2] This chronic inflammatory skin disease causes highest disability-adjusted life year (DALY) score (128.7 per 100,000 people) amongst all skin diseases, placing it as the 21st cause of non-fatal burden among all diseases. The exact cause of AD is still unknown, but novel studies suggest that both (epi) genetic and environmental facts including recent identified microbiome may play an important role in natural course of AD.[3] The diagnosis may sometimes be challenging and atopic dermatitis may resemble other types of dermatitis as well as other skin diseases such as psoriasis, infections, infestations and malignancies as well as metabolic, genetic and autoimmune disorders. [4]. The standard symptomatic AD treatment includes hydration, restoration of the skin

barrier, control of skin inflammation, and treatment of secondary infections.[4, 5] Topical corticosteroids remain the first-line medical treatment for the control of symptoms, but relapses are common [6] and adverse effects limit their chronic use. [7] Calcineurin inhibitors are sometimes effective in reducing inflammation and help spare the use of topical steroids. [8] Besides pharmacological symptomatic treatment recent strategies are move towards immunomodulatory approaches. At present there are a number of trails underway to explore the role of immunomodulatory factors such as prebiotics (soluble dietary fibre) and probiotics, which may restore more favorable gut colonization for optimal immune maturation. Early environmental exposures have long lasting effects on many aspects of growth and development and the most, effective strategies for allergy prevention must begin early in life, even prenatal. Skin barrier maintenance, early diet and probiotics/synbiotics/gut microbiome represent. Probiotics are live microbes which benefits and positive effects on human health if they use in adequate quantities. [9, 10]

Word probiotic comes from a greek word pro+bios that means "for life" and it is used for the first time in 1953. [11] Lactobacilus rhamnosus GG strain is one of the most investigated bacteria strain.

It was discovered by two scientists Shervud Gorbach and Bari Goldin in 1983.

Probiotic supplementations were performed mainly in high risk families during gestation (mostly during the last trimester) and/or during the first 6 months of life. In a systematic review and meta-analysis mixtures of probiotics, including Lactobacillus, Bifidobacterium and Propionibacterium strains significantly decreased the risk of AD if given pre- and postnatally. [12-14]

2. Method

2.1. Material and Methods

Our study was a real life controlled observational study. The study was conducted in the Children's Hospital for Lung Diseases and Tuberculosis, Medical Centre "Dr Dragiša Mišović", Belgrade, Serbia. The protocol was approved by the Ethical Committee of the hospital. Informed consent was obtained from all parents or caregivers of the participants. The active group was addressed to probiotic strain Lactobacillus rhamnosus $1x10^{10}$ cfu/g pro doses with 0.01mg of vitamin D3 and 0.6mg zinc (BebiCol® with zinc probiotic drops Abela farma, Serbia) and standard pharmacological treatment, whereas the control group undertook standard pharmacological treatment only. Patients were considered eligible for probiotics treatment according to the following factors: atopic dermatitis (fullfiled critera) Seymore criteria - Table 1, age range between 6 months and 3 years old, positive family history for atopic diseases, without antihistamines in the last 14 days, without local and/or systemic corticosteroids in the last 14 days. BebiCol® with zinc probiotic drops (Approved by the Ministry of Health of the Republic of Serbia. Certificate number: 12071/2018 since February 6, 2018 produced by Serbian National Company Abela pharma, Belgrade). BebiCol® with zinc contains Lactobacillus rhamnosus GG one of most thoroughly studied probiotic strains in the world in an effective dose of $1x10^{10}$ cfu/g Furthermore, BebiCol® with zinc probiotic drops contain both vitamin D3 and zinc. Zinc is recommended by The World Health Organization and UNICEF as an integral part for treating diarrhea. Vitamin D3 is recommended to all babies for the first twelve months by The European Society for Pediatric Gastroenterology, Hepatology and Nutrition and The World Health Organization.

According to the manufacturer recommendation patients received 14 drops of BebiCol® with zinc 14 drops once a day. We advice patients to shake the bottle vigorously before each dose. Opalescent quality of the drops after shaking the bottle is common and expected. It is best to take the drops by using a spoon. The drops can be taken by mixing them with either food or drinks. Pipettes should not be used to mix BebiCol® drops with other liquids or food. Patients from both groups (irrespective to probiotic strain Lactobacillus rhamnosus) received an appropriate pharmacological treatment according to guidelines: hydration, restoration of the skin barrier, control of skin inflammation, and treatment of secondary infections [10, 14], topical corticosteroids, calcineurin inhibitors.

The aim of the current study was to assess the effect of oral supplementation with LGG in infancy on eczema development and sensitization during the first 2 years of life.

2.2. Clinical Evaluation

All patients were followed up during the 6 months from the beginning of the protocol.

The following symptoms of AD - SCORAD Severity Scoring for Atopic Dermatitis were scored: redness, swelling, crusting, scratch marks, skin thickening (lichenification) and dryness. Parents were asked to fill in the symptom and medication score diary during a follow up period. The following symptoms for allergic rhiniconjuctivits were scored: redness, swelling, dryness, itching. Symptoms of bronchial hyperactivity and postnasal drip were followed up.

Each symptom was scored as 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and the mean monthly symptom score (SS) was calculated. The use of symptomatic medications was also recorded daily, during the same period.

2.3. Statistical Analysis

The sample size was calculated with the software package G power. A sufficient number of observation units for the error level $\alpha=0.05$ and power of the study $1-\beta=0.8$ is 0.72 were considered. Descriptive and analytical statistical methods were used. The following descriptive variables were described: measures of central tendency (mean, median), measure of dispersion (standard deviation, interval of variation). Analytical statistical methods were used to test differences, parametric and nonparametric variables.

Student's t test and analysis of variance of repeated measurements were used. Chi square test, McNemar test, Mann–Whitney test, Wilcoxon test, Friedman test were also included. All data were analyzed in SPSS 15.0 software package. (SPSS Inc., Chicago, Illi- nois, USA).

2.4. Ethical Consideration

Ethical approval was obtained from the institutional review board of University Clinical Centre "Dr Dragiša Mišović", Belgrade, Serbia. the before conducting the research. Patient consent was obtained from each parents or caregivers.

3. Result

Overall 96 patients were included: 52 (16 girls and 36 boys) received probiotics as an add-on to standard AD treatment and 44 (19 girls and 25 boys) treated according to standard protocols for AD. Patients from experimental and control group were homogenous for all demographic characteristics and positive family history for allergic diseases.

Regarding the treatment: 22 infants in experimental and 18 infants in control group were treated with local corticosteroids, no statistical difference at a baseline. Contrary we found statistically significant differences between those two groups regarding standard antiallergic and anti asthmatic pharmacological treatment. Patients in a control group used statistically significant more antihistamines, inhaled corticosteroids and leucotriens inhibitors.

No statistical significant differences observed regarding the way of delivery (vaginal vs cesarian section) and breast-feeding and milk formula usage. At the baseline statistical significant was observed between two groups regarding SCORAD as well as for asthma and nasal symptom score. SCORAD score was statistically significant higher in probiotic groups comparing with controls. It is a very interesting to point out that there is a changes in SCORAD between the groups. When we divided patients in groups we have observed SCORAD changes between the groups, we observed a statistically significant differences during the follow up period in experimental group (p<0,001), where as no statistically significant differences was observed in control group (p=0,564).

Table 1. *SCORAD score Graf 1. SCORAD score.*

		Group					P value
		Mean	**SD**	**Median**	**Perc. 25**	**Perc. 75**	
SCORAD score	Bebicol	8.13	3.61	8.50	5.50	11.00	<0.001 MW
	Control	4.27	4.23	2.00	1.00	6.50	
Control 1 SCORAD	Bebicol	1.25	1.31	1.00	.00	2.00	<0.001 MW
	Control	4.30	4.25	2.00	1.00	6.50	
Delta SCORAD	Bebicol	6.88	3.10	7.00	5.00	8.50	<0.001 MW
	Control	-.02	.26	.00	.00	.00	

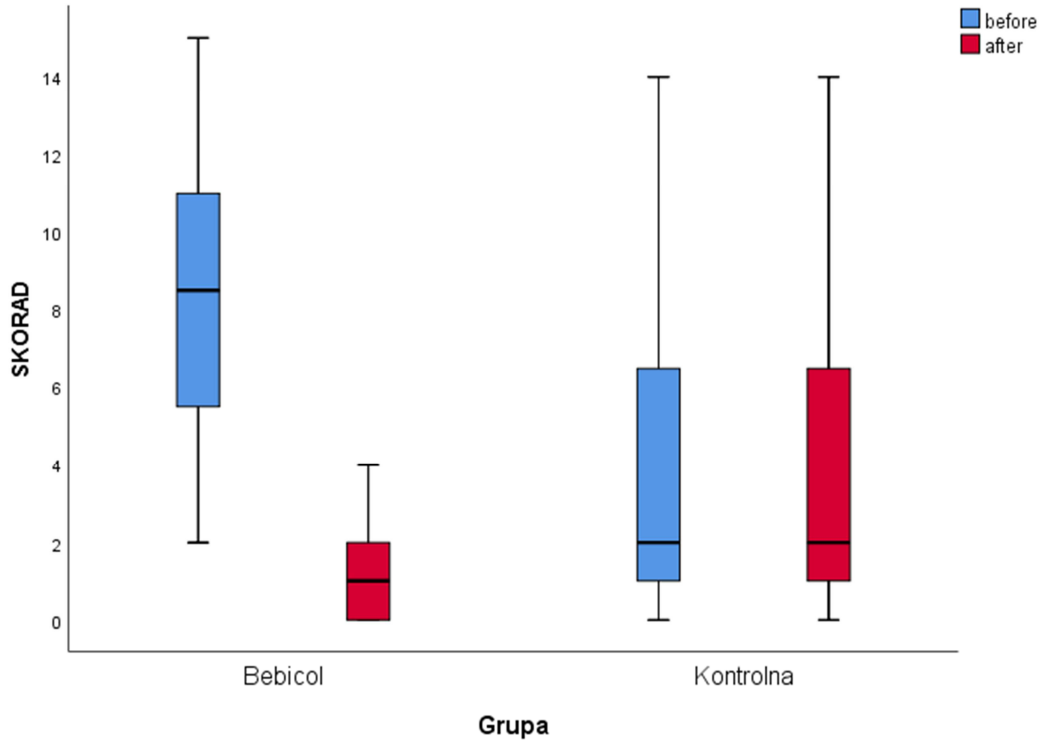

Figure 1. *SCORAD score in Bebicol and control group.*

4. Discussion

A great number of review and meta-analysis evaluated efficacy of Lactobacillus rhamnosus GG (LGG) supplementation prenatally and/or postnatally for the primary prevention of eczema. Three main protolerogenic mechanism of action have been described. [15]. World Allergy Organization (WAO) [16] did not recommend use of probiotics for reducing the risk of allergy in children in its paper from 2015. However the WAO considered that there is a likely net benefit from using probiotics for preventing eczema. Specifically, the WAO suggests: "(a) using probiotics in pregnant women at high risk for having an allergic child; (b) using probiotics in women who breastfeed infants at high risk of developing allergy; and (c) using probiotics in infants at high risk of developing allergy". All recommendations were conditional and supported by a very low quality of evidence. Since the beginning, these guidelines raised a debate [17], mainly because of the lack of answers to practical questions such as: Which probiotic (s) should be used to reduce the risk of eczema? When should one start the administration of probiotics with proven efficacy? When should one stop? What is the dose of an effective probiotic [7] The finding of this study showed that Lactobacillus rhamnosus LGG probiotic strain (BebiCol® with zinc probiotic drops) was effective in decreasing severity score of atopic dermatitis. In this study Lactobacillus rhamnosus LGG probiotic strain (BebiCol® with zinc probiotic drops) had also an impact on reducing the usage of local and systemic antiallergic and anti immflammatory drugs which is more or less comparable with previously conducted studies by Kalliomäki (18) The result of this study disclosed that probiotics given during the infancy and early childhood can reduce clinical manifestations of atopic dermatitis. The finding are contrary to those from Cabana et al. study in which LGG was administered to infants and reported no significant difference between groups in the risk of eczema up to 2 years of age (RR 0.93 (0.59, 1.45)). (19) In other 5 RCTs there were also no statistical difference between the LGG-supplemented and control groups in the risk of eczema, regardless of the timing of LGG administration, up to 2 years (RR 0.90 (0.67, 1.21), I2=45%). [18-22]

A 2015 systematic review by Cuello-Garcia et al. supported our findings. [23] In this systemic review 29 publications identified in which 12 various probiotics, single or in combinations, were used. They concluded that there are significant benefits of probiotic supplementation in reducing the risk of eczema when used by women during the last trimester of pregnancy (RR 0.71, 95% CI 0.60 to 0.84), when used by breastfeeding mothers (RR 0.57, 95% CI 0.47 to 0.69), or when given to infants (RR 0.80, 95% CI 0.68 to 0.94). [23, 24]

Furthermore trying to answer the question which is the best probiotic strains and combination is the most effective to improve clinical manifestation of atopic dermatitis, in our study we have decided to treat patients with Lactobacillus rhamnosus LGG strain in combination with zinc and vitamin D3. In our opinion this is one of the most adequate combination because as it has been previously mentioned LGG has been proven to have positive effects on atopic dermatitis. According to some hypothesis the deficiency of vitamin D3 as well as the lack of Zn can be a predisposing factors for allergic disease development. [25]

In Gray and coauthors systemic review and metaanalysis it has been showed that zinc can play a central role in skin integrity via barrier and immune mechanisms and may also be relevant in the pathogenesis of atopic dermatitis (AD). We conclude that low serum, hair and erythrocyte zinc. [26]

5. Conclusion

In conclusion, this study has found that Lactobacillus rhamnosus GG (LGG) formulation with Zn and vitamin D3 supplementation during the postnatal period (in infancy and early childhood) reduce the severity of atopic dermatitis. Type of delivery, type of feeding breast-feeding versus adapted milk formulas were not found to be to be statistically associated with risk of atopic dermatitis. Based on the findings it is recommended to introduce probiotic supplementation as well as vitamin D3 and zinc in infants and children with atopic dermatitis and positive family history.

Author Contribution

IDF and ZZ conceived and designed the study, and coordinated the data collection. OO and ML revised the study results and drafted the manuscript. VV and ML contributed to data interpretation and manuscript preparation. All authors read and approved the final manuscript.

Conflict of Interest Statement

The authors declare no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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