

Efficacy of Specially Formulated Combination Three Probiotic Strains with Vitamin D3 and Zn in Children with Atopic Dermatitis

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Abstract: Introduction: Atopic dermatitis (AD) is a chronic inflammatory, pruritic and relapsing skin disease, frequently originated in infants and young children. The objective of our study was to evaluate the clinical efficacy and quality of life in children with AD who were treated with mixture of 3×10^9 CFU of 3 probiotic strains Lactobacillus Casei BL 2401, Lactobacillus Salivarius BL 2201, Bifidobacterium Breve BL 3406 in combination with 7mg Zinc in Hypro-ri form for better resorption and 1200 IJ Vitamin D3, once per day for 3 months. Method: This prospective case control study was conducted in the University Hospital "Dr Dragiša Mišović", Belgrade, Serbia, Hospital for Children's Hospital for Lung diseases and Tb. The study enrolled 150 patients with AD aged between 3 and 17 years. 75 participants received the treatment: mixture of 3×10^9 CFU of 3 probiotic strains Lactobacillus Casei BL 2401, Lactobacillus Salivarius BL 2201, Bifidobacterium Breve BL 3406 in combination with 7mg Zinc in Hypro-ri form for better resorption and 1200 IJ Vitamin D3, once per day for 3 months as an add-on to standard AD treatment and 75 of them were treated according to standard protocols for AD. Results: There is a statistically significant difference in SCORAD value before and after the treatment between the groups. Discussion: Our study was the first that assess the efficacy of a mixture of 3×10^9 CFU probiotic strains Lactobacillus Casei BL 2401, Lactobacillus Salivarius BL 2201, Bifidobacterium Breve BL 3406 in combination with 7mg Zinc in Hypro-ri® form for better resorption and 1200 IJ Vitamin D3 in children with atopic dermatitis. Our study confirmed that regular treatment with this specific probiotic mixture significantly decreased pruritus and sleep problems and improved quality of life in highly atopic children with severe atopic dermatitis.

Keywords: Children, Atopic Dermatitis, Probiotics

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory, pruritic and relapsing skin disease predominantly affecting pediatric population and commonly associated with other atopic diseases such as food allergy and asthma [1]. Our

understanding of the underlying pathophysiologic mechanism of AD has changed over the years. Multiple factors are involved in the development of AD including genetics, atopy, impaired skin barrier, dysregulated immune function and dysbiosis in the gut and/or skin. [2] The skin itself represent the first line barrier between the body and surrounding

environment, preventing antigens from stimulating immune response. Skin barrier could be physically impaired due to a low level of lipids (ceramides and sphingosines) or/and abnormal keratinization due to dysfunctional filaggrin (a main component of the *stratum corneum*). [3] Ziyab et al. found that increased filaggrin expression is associated with a reduced risk of AD during the first year of life. [4] Some early studies showed that filaggrin loss-of-function mutations could be detected in about 20% of European patients with atopic dermatitis. An abnormal response to environmental irritants leads to the Th2 cytokines production such as IL13 and thymic stromal lymphopoietin (TSLP) further promoting the susceptibility to *Staphylococcus Aureus* colonization (Golden Staph.) [5, 6] TSLP may also act as a trigger of bronchial hyper-reactivity; when depleted in mice, the atopic march is stemmed, suggesting that TSLP may be a link between AD and asthma. [7] Recent studies showed that a specific interaction between AD and microbial imbalance as well as abnormal cutaneous immune response to microorganisms in children with AD could be involved in the pathways leading to the development of atopic dermatitis and other allergic diseases. [8, 9]

Of note microbial infants' colonization starts before birth and continues into childhood through exposure to environmental factors. It is currently known that the mother transfers microorganisms to the newborn through the placenta, intestine, meconium, and vagina. The meta analysis by Goffau et al. showed the existence of a low biomass placental microbiota in healthy pregnancies mostly consist of *Lactobacillus*, *Ureaplasma*, *Fusobacterium*, *Staphylococcus*, *Prevotella* and *Streptococcus* genera. [10] Infant gut microbiota is affected by diverse prenatal, perinatal and early neonatal conditions including time and mode of delivery, nutrition (breast-feeding vs adopted milk formulas), maternal and/or antibiotic usage in neonatal period. [11]

It is known for decades that newborns from vaginal delivery have a greater variety of bacterial flora and a higher amount of *Bifidobacterium*, *Bacteroides*, and *Lactobacillus* compared to those born by caesarean delivery. [12-14] Current data suggest that gut dysbiosis, especially if it occurs early in life, could substantially contribute to the development of inflammatory condition such as allergies.

Unlike other chronic inflammatory conditions, allergic diseases start early in life or even prenatally, as we have already mentioned. Atopic dermatitis usually represents the first step of atopic march, commonly preceding other allergic conditions (food and respiratory allergies). AD characterized mainly with redness, itching and pruritus of the skin that is responsible for much of the disease burden, significantly impacting on patients and their families' quality of life. [15, 16] The main treatment protocols include topical anti-inflammatory medications and skin moisturization; however, depending on AD severity, patients may require systemic therapy such as biologics or immunosuppressive drugs [17]. Patients' adherence to treatment, disease severity, cost & access, corticosteroid phobia, triggers identification, treatment side effects, and lack of the appropriate medications

for children were major challenges for AD management. Although current evidence doesn't fully support probiotics and vitamins supplementation in prevention and treatment of AD, this combination can be promising especially within a personalized approach to AD treatment. The objective of our study was to evaluate the clinical efficacy and quality of life in AD children treated with mixture of 3 x 10⁹ CFU of 3 probiotic strains *Lactobacillus Casei* BL 2401, *Lactobacillus Salivarius* BL 2201, *Bifidobacterium Breve* BL 3406 in combination with 7mg Zinc in Hypro-ri form for better resorption and 1200 IJ Vitamin D3, once per day for 3 months (Registration number of the product IMUNOLAK Kids D3 Zn 18660-2021 since 13.05.2021).

2. Method

2.1. Material and Methods

This prospective case control study was conducted in the University Hospital "Dr Dragiša Mišović", Belgrade, Serbia - Hospital for Children Pulmonary Disease and TBC. The study included 150 patients with AD aged between 3 and 17 years. 75 participants received the treatment consist of mixture of 3 x 10⁹ CFU of 3 probiotic strains *Lactobacillus Casei* BL 2401, *Lactobacillus Salivarius* BL 2201, *Bifidobacterium Breve* BL 3406 in combination with 7mg Zinc in Hypro-ri form for better resorption and 1200 IJ Vitamin D3, once per day for 3 months as an add-on to standard AD treatment and 75 of them were treated according to standard protocols for AD.

2.2. Clinical Evaluation

All patients were followed up for 3 months on a monthly base from the beginning of the protocol. The clinical evaluation included: - SCORAD Severity Scoring for Atopic Dermatitis were scored, a validated index assessing redness, swelling, crusting, scratch marks, skin thickening (lichenification) and dryness.; - medication score, by evaluating the use of symptomatic medications; - VAnalogic Scale (VAS) for sleep problems (disorder), itching, influence of the disease on child's mood and physical activity at the baseline and after the treatment course. During the follow up period we have evaluated the satisfactory of parents and/or caregivers regarding treatment satisfaction. They were supposed to answer if they were satisfied with AD treatment and to state what are the reasons for being unsatisfied.

2.3. Statistical Analysis

The sample size was calculated with the software package G power. 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 analysed in

SPSS 15.0 software package. (SPSS Inc., Chicago, Illinois, USA).

2.4. Ethical Consideration

Ethical approval was obtained from the institutional review board of University Hospital “Dr Dragiša Mišović”, Belgrade, Serbia before conducting the research. Patient consent was obtained from each parent or caregivers.

3. Results

Patients from the experimental and control group were homogenous for all demographic characteristics and positive family history for allergic diseases. The participants were divided in two groups age 3-6 and age 7-17 years old, no

differences between the groups according demographic characteristics. Significant differences were noticed only regarding the gestational week and type of delivery. Children in experimental group were born in lower gestational week in comparison to the patients in a control group. They were more frequently delivered via caesarean session. Patients in the experimental group were introduced solid food later than those in control group. A great majority of children were diagnosed atopic dermatitis in the first year of life 62 (82.7%) in experimental and 56 (74.7%) in control groups, no statistical differences between the groups. Almost half of the overall participants had positive family history for atopic dermatitis, 50.7% in probiotic (experimental) group vs 41.3% in control group. (Table 1).

Table 1. Sociodemographic characteristics.

		Group				p value
		Experimental		Control		
		N	%	N	%	
Age	3-6	39	52.0%	28	37.3%	0.071 ^a
	7-17	36	48.0%	47	62.7%	
Gender	Female	29	38.7%	38	50.7%	0.139 ^a
	Male	46	61.3%	37	49.3%	
Age when AD was first diagnosed	0-1	62	82.7%	56	74.7%	0.466 ^b
	2-5	9	12.0%	15	20.0%	
	6+	4	5.3%	4	5.3%	
AD in family	da	38	50.7%	31	41.3%	0.251 ^a
	ne	37	49.3%	44	58.7%	
Gestation week	< 37	7	9.3%	0	0.0%	0.013 ^b
	37+	68	90.7%	75	100.0%	
Type of delivery	S.C.	30	40.0%	9	12.0%	<0.001 ^a
	Vaginal	45	60.0%	66	88.0%	
	4	21	28.0%	7	9.3%	
Introduction of solid food	5	13	17.3%	30	40.0%	<0.001 ^a
	6	41	54.7%	38	50.7%	

a: Pirsonov hi2 test; b: Fisher test/Fisher-Freeman-Halton test; c: Mann-Whitney U test

Regarding parental treatment satisfaction 64 (85.3%) parents in experimental group and 48 (64%) parents in a control group were partially satisfied with AD treatment. Only one patient in experimental, intervention... group and 27 were satisfied, whereas 10 parents in experimental and no parents in control group were unsatisfied. Statistically significant difference was observed between two groups $p < 0.001$. Statistically significant difference in parental satisfaction, poor response and rapid deterioration were observed. The frequent use of corticosteroids is at the very border of the conventional level of significance, so

it should be taken into account when interpreting the results. The main reason for unsatisfactory is rapid deterioration after cessation of the treatment observed in 69 of the participants in the experimental and in 43 participants in control group. A statistically significant difference between two groups was noticed $p < 0.001$. Frequent usage of local (dermal) corticosteroids and poor response to the treatment were not reasons for parents to be unsatisfied with the treatment. There are no statistical differences among observed groups (Table 2).

Table 2. Treatment satisfaction.

Parental treatment satisfaction	Satisfied	1	1.3%	27	36.0%	<0.001 ^a
	Partially satisfied	64	85.3%	48	64.0%	
	Unsatisfied	10	13.3%	0	0.0%	
Poor response	No	65	86.7%	73	97.3%	0.016 ^a
	Yes	10	13.3%	2	2.7%	
Rapid deterioration after cessation of the treatment	No	6	8.0%	32	42.7%	<0.001 ^a
	Yes	69	92.0%	43	57.3%	
Frequent usage of local corticosteroids	No	70	93.3%	75	100.0%	0.058 ^b
	Yes	5	6.7%	0	0.0%	

a: Pirson hi2 test bFisher test

We found clinical improvement in the experimental group, demonstrated by statistically significant decrease of SCORAD after the treatment. SCORAD decreased significantly in all the three measurements during probiotic course (intervention). During the (In) follow up period significant differences between the groups were observed. Patients in the

experimental group had significantly higher values of SCORAD in all measurements. When we compared the values in each group independently, we found only significant reduction in the experimental group.-SCORAD before and after the treatment.

Table 3. SCORAD before and after the treatment.

		Group					p value
		Mean	SD	Median	P25	P75	
SCORAD 1	Experimental	53.17	14.38	52.05	42.70	65.10	<0.001 ^a
	Control	16.23	13.53	10.00	8.00	20.00	
SCORAD 2	Experimental	19.46	10.04	17.85	13.40	23.15	0.166 ^a
	Control	20.25	16.30	14.99	8.00	29.00	
Δ SCORAD	Experimental	-33.71	14.17	-33.25	-43.25	-25.40	<0.001 ^b
	Control	4.03	10.71	2.00	-1.70	5.00	

a: Mann-Whitney U test b: Student t test

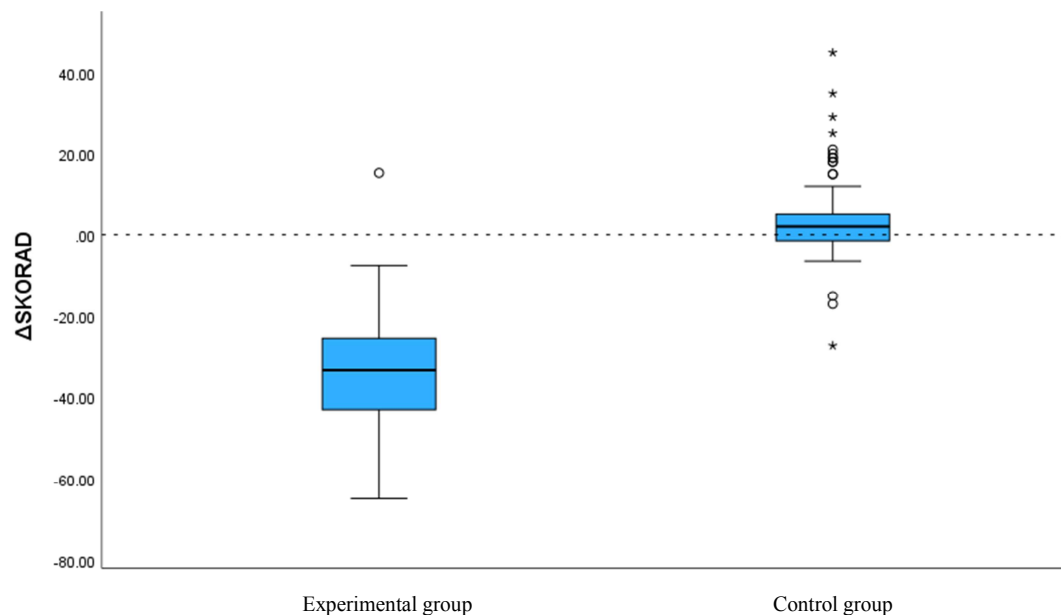


Figure 1. SCORAD before and after the treatment experimental and control group.

There is a statistically significant difference of SCORAD value before and after the treatment between the groups.

Table 4. VAS-Visual Analog Scale before and after the treatment.

		Group					p value
		Mean	SD	Med	P25	P75	
VAS Sleep 1	Experimental	5.51	1.98	5.0	4.0	7.0	<0.001
	Control	1.77	1.90	1.0	.0	4.0	
VAS Sleep 2	Experimental	1.59	1.53	1.0	.0	3.0	0.084
	Control	2.56	2.63	1.0	.0	5.0	
Δ VAS Sleep	Experimental	-3.92	1.93	-4.0	-5.0	-3.0	<0.001
	Control	.79	1.39	.0	.0	1.0	
VAS Physical Activity 1	Experimental	2.37	2.07	3.0	.0	4.0	<0.001
	Control	.96	1.16	1.0	.0	2.0	
VAS Physical Activity 2	Experimental	1.63	1.45	2.0	.0	3.0	0.051
	Control	1.19	1.48	1.0	.0	2.0	
Δ VAS Physical Activity	Experimental	-.75	1.40	.0	-2.0	.0	<0.001
	Control	.23	.98	.0	.0	.0	
VAS Pruritus 1	Experimental	6.80	1.91	7.0	6.0	8.0	<0.001
	Control	3.08	1.78	3.0	2.0	4.0	
VAS Pruritus 2	Experimental	2.37	1.51	2.0	1.0	3.0	<0.001
	Control	3.80	2.25	3.0	2.0	6.0	

		Group					p value
		Mean	SD	Med	P25	P75	
ΔVAS Pruritus	Experimental	-4.43		2.34	-5.0	-6.0	<0.001
	Control	.72		1.43	.0	.0	
VAS Mood 1	Experimental	3.53		2.61	4.0	1.0	<0.001
	Control	.97		1.37	.0	.0	
VAS Mood 2	Experimental	1.99		1.47	2.0	.0	0.002
	Control	1.33		1.77	1.0	.0	
ΔVAS Mood	Experimental	-1.55		2.02	-1.0	-3.0	<0.001
	Control	.36		.95	.0	.0	

3 months of probiotic mixture treatment combined with vitamin D3 and Zinc improved significantly all quality-of-life parameters on VAS. Table 4. Our study confirmed that regular treatment with specific probiotic mixture significantly decreased pruritus and sleep problems and improved quality of life in highly atopic children with serious forms of atopic dermatitis.

4. Discussion

Our study confirmed that regular treatment with probiotics significantly decreased pruritus and sleep problems and improved quality of life in highly atopic children with serious forms of atopic dermatitis. Up to now several studies evaluated the clinical efficacy of probiotics with or without D3 and/or Zn in prevention and treatment of atopic dermatitis in pediatric population.

Wang et al. meta analysis evaluated prevention effects of probiotic on AD. According to their data *Lactobacillus rhamnosus* is the most commonly studied single strain. [18] The great majority of papers studied the possibility of probiotics intervention prenatally (> 36 weeks of gestational age) and postnatally. Subgroup analysis showed that probiotics were effective when the intervention recipients were mothers and infants, when the timing of the intervention was prenatal and postpartum, when probiotics used were *Lactobacillus rhamnosus* and mixed strains, and when the follow-up time was less than 2 years. On the other hand, Fijan et al. demonstrated that the supplementation with single-strain lactobacilli for treating AD in children decreases the SCORAD index [19]. Most studies investigated (*Lactobacillus*) *rhamnosus* GG; supplementation was mainly done for 3 or 4 months. Findings showed a significant decrease in the SCORAD index but with high heterogeneity between the studies. Similarly, two recent meta-analyses evaluated the effect of probiotics as treatment in adult patients with AD. Umborowati et al. found probiotics can improve severity in patients with moderate AD, evidenced by decreased SCORAD index. [20].

Those results are in accordance with the results from our study that also showed an improvement in SCORAD in pediatric patients with mild to moderate atopic dermatitis after 3 months treatment with three probiotics strains in combination with D3 and Zn.

Li et al. evaluated the effect in the short-term (< 4 weeks) and long-term (> 8 weeks) after probiotics administration [21]. According to their findings a decreased severity in the short

and long term could be observed. Subgroup analysis showed decreased severity based on SCORAD and better effect with oral and mixed probiotics in the short term, while decreased severity for oral and single strain probiotics in the long term. They also found that a mixture of *Lactobacillus salivarius* (LS01) and *Bifidobacterium* (BR03) have a high probability of best supplementation in the short and long term. According to the World Allergy Organization (WAO) position paper probiotics are not generally recommended in prevention of allergic diseases, although it is stated that probiotics could be used in three categories of patients with high risks (a) pregnant women at high risk for having an allergic child (a child with allergies); (b) women who breastfeed infants at high risk of developing allergy; and (c) infants at high risk of developing allergy". [22] As mentioned in the introduction children with atopic dermatitis could be considered to be at high risk to develop other allergic diseases such as allergic rhinitis and asthma. They are ideal candidates to receive probiotics for both treatment and further prevention of atopic marsh.

Although an increased awareness of the importance of microbiome dis-balance in AD pathogenesis, there is still no protocol for probiotics in atopic dermatitis and a majority of studies investigated a single probiotic strain in AD patients. Our study was the first that included a mixture of 3 x 10⁹ CFU of 3 probiotic strains *Lactobacillus Casei* BL 2401, *Lactobacillus Salivarius* BL 2201, *Bifidobacterium Breve* BL 3406 in combination with 7mg Zinc in Hypro-ri® form for better resorption and 1200 IJ Vitamin D3 in children with atopic dermatitis.

According to similar studies [23] we chose to limit the duration of the trial to three months as we thought that this was a long enough time for clinicians to observe results of the intervention and for patients to wait for results; according to the data longer follow up often increase the risk for drop off. however, longer studies may be useful in the future. The evaluation of the effects on AD is difficult and there is no gold standard. However we found clinical improvement in the experimental group, demonstrated by statistically significant decrease of SCORAD. Also it would very important to continue the follow up for at least two years in order to evaluate the onset of comorbidities such as food allergies and asthma. Pruritus as a main symptom of AD that impair the quality of life of children or/and their caregivers showed a significant improvement as well as the all other QoL parameters on VAS, particularly in highly atopic children. [24-26]

5. Conclusion

Atopic dermatitis is the most common chronic inflammatory skin disease in infants and young children, with a great impact on health care system and quality of life of the affected patients and/or their parents and/or caregivers.

Positive family history observed in almost half of the included patients can't be changed, but fortunately we are able to accepted healthy life style including adequate skin care, nutrition rich in omega3 fatty acids and fibers as well as the usage of combination of probiotics and vitamins.

This study has found that supplementation with mixture of 3×10^9 CFU of probiotic strains *Lactobacillus Casei* BL 2401, *Lactobacillus Salivarius* BL 2201, *Bifidobacterium Breve* BL 3406 in combination with 7mg Zinc in Hypo-ri[®] form for better resorption and 1200 IJ Vitamin D3 in children with moderate and severe form of atopic dermatitis improved SCORAD after 3 months of treatment. We have also showed a significant improvement of quality of life presented on VAS during the follow up period. Although there is no protocols for probiotics for children with atopic dermatitis, we have found that mixture of adequate specific probiotic strains in combination with D3 and Zn could be used as add on treatment.

Author Contribution

IF and ZZ conceived and designed the study, and coordinated the data collection. OO, VV, SM and MC revised the study results and drafted the manuscript. VV and OO 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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