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RANDOMISED CLINICAL TRIAL: THE EFFECTIVNESS OF IMMUNONUTRIENTS IN INFANTS WITH INFLAMMATORY BOWEL DISEASES

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Background: *At present, there are considered new approaches in treatment of IBD in infants. The mail goal is to contribute to therapeutic benefit with rational, physiologic, and nontoxic approach. Recently, probiotics, prebiotics and n-3 LC PUFA were found to have a potential relationship with IBD pathophysiology. As immunonutrients, their simultaneous application can enhance the therapeutic effect; contribute in reducing the severity of IBD, achievement of favorable course of inflammation and maintenance remission. So far few studied were perform in this way.*

Goals: *To assess the effectiveness of simultaneous application of immunonutrients (probiotics, prebiotics and n-3 LC PUFAs) in the treatment of chronic non-specific non-ulcerative colitis in infants.*

Methods: *A total of 92 infants (mean age 1.6 years, range 1–3 years, female/male 10/13) with chronic non-specific non-ulcerative colitis (CNNC) were randomized into two groups: 50 infants (main group) received иммунонутриенты, and other 42 children were control group in conjunction with conventional therapy. Clinical evaluation, endoscopic investigations as well as expression levels of pro-and anti-inflammatory interleukins and microbiologic analyses of faecal samples (Bifidobacteria, Lactobacilli) were evaluated at the beginning and at the end of the trial.*

Results: *Summarising the results of the study, the Disease Activity Index (DAI) score decreased significantly in the main group (3.4±1.2 versus baseline 8.6±0.8, P < 0.01) compared to control group (7.1±1.1 versus baseline 8.7±0.7, P > 0.05). All patients of the main group and 25 of 42 (59,5 %) infants of control group had a clinical response (P < 0.05), whereas remission was reached in 47 of 50 (95 %) infants of the main group and in 22 of 42 (52,4 %) infants of control group (P < 0.05). In both groups no exacerbation occurred. There were no clinical adverse events related to immunonutrient applications. , were observed interleukine and significant imbalance of indigenous intestinal microflora. At the post-trial evaluation significant improvement of immunologic and bacteriologic paramiters was observed only in infats of the main group (P < 0.01).*

Conclusions: *The data of the study document the efficacy of application of immunonutrients (probiotics, prebiotics and n-3 LC PUFAs) as an accompanying treatment in improving clinical manifestation of the disease, redusing disease activity and mucosal inflammation in infants with chronic non-specific non-ulcarative colitis as well as positive changes in the expression levels of pro- and anti-inflammatory cytokines involved in the mechanisms of IBD and increasing indigenous bacteria. This clinical randomized trial demonstrated the role of immuninutrients in maintenance of remission chronic inflammatory deseases in infants.*

Keywords: *inflammatory bowel diseases, infants, immunonutrients.*

Introduction

The incidence and prevalence of inflammatory bowel diseases (IBD) are increasing with time and in different regions around the world, indicating its emergence as a global disease. IBD is believed to be associated with industrialization of nations, with the highest incidence rates and prevalence of IBD predominantly in the countries of Europe, including Ukraine. Regarding infancy there is an increasingly recognized problem as well [8].

The inflammatory bowel diseases (IBDs), consisting of ulcerative colitis (UC) and Crohn's disease (CD), are mostly observed in adults [21]. It should be emphasized that in infants the occurrence of severe pathologic conditions like CD and UC is rare, that do not exclude onset and development of chronic intestinal inflammation with clinical features characterized for earlier period of life.

Although it is considered, according to published data from epidemiological studies that incidence of IBD in infants is not so elevated compared with adult population, in our opinion it seems that this pathology is underestimated in infants due to some reasons: clinical symptoms and signs are scared; manifestation can appear as functional bowel disorders that mimic IBD; more frequently is used the term of «dysbiosis; clinicians do not pay enough attention to IBD diagnosis in infants. Nowadays, IBD in infants with its own clinical features and typical mucosal changing in the course of intestinal inflamation is considered as chronic non-specific non-ulcarative colitis. This diagnosis was approved by pediatric assocoition of Ukraine and presented in new classification of digestive tract disesases.

IBD with onset in this age group is likely a heterogeneous group of disorders, and as such, there is variability in the clinical presentation. It appears that, when compared to elder children and adults, infants are more likely to demonstrate colonic involvement, i.e. in regions of the gut most highly colonized by bacteria. Inflammation involves only the superficial layers of the intestinal mucosa along the large bowel. But because of earlier beginning of inflammatory intestinal disorders in infants with immature intestinal tract and immune system on the phase of earlier development, such alteration may lead to increased risk for development more severe consequences and poor prognosis later in life.

The etiology of IBD has been extensively studied in the past few decades; however, the pathogenesis is not fully understood.

There is obvious evidence that dysregulation of the mucosal immune system is a major factor contributing to the pathogenesis of IBD [30]. The study in recent years indicate, that pathogenesis of these diseases represents the outcome of three essential, interactive co-factors: host susceptibility, enteric microflora and mucosal immunity [27]. The basis of IBD is the presence of genetically determined alterations resulting in a mucosal immune system that overreacts to normal intestinal microflora. These immune responses may be

induced by defects in the epithelial barrier, and increased intestinal permeability, adherence of bacteria, and decreased expression of protective intestinal components [6]. The mucosal immune system interacts with the local microenvironment, recognizing and avoiding reactions to commensal microflora (tolerance), whilst retaining its capacity to respond to episodic challenge from pathogens [25].

To date, increased synthesis and release of pro-inflammatory mediators such as cytokines, chemokines, eicosanoids, as well as other immune abnormalities are assumed as the main mechanism in IBD pathogenesis. [3]. In this regard, development of IBD is a result of dysregulated mucosal response in the intestinal wall facilitated by defects in epithelial barrier function and mucosal immune system with excessive production of cytokines and other aggressive molecules, resulting in tissue injury.

At present, there is also considered the hypothesis in which changes in mucins imposed by immunological or microbial factors may contribute to the development and/or perpetuation of chronic intestinal inflammation. Alterations in both membrane-bound and secretory mucins have been described involving genetic mutations in mucin genes, changes in mucin mRNA and protein levels, degree of glycosylation, sulphation, and degradation of mucins. As mucins are strategically positioned between the vulnerable mucosa and the bacterial contents of the bowel, changes in mucin structure and/or quantity probably influence their protective functions and therefore constitute possible aetiological factors in the pathogenesis of IBD [19]. This hypothesis, however, is difficult to prove in humans and needs detailed analysis of those aspects of mucins necessary for protection against disease.

Significant amount of scientific evidence implicates intestinal microbiota in the pathogenesis of IBD. An emerging consensus hypothesis is that intestinal dysbiosis (microbial imbalance) may be a trigger for IBD, i.e. the development of IBD might be due to an altered immune response and a disrupted mechanism of host tolerance to the non-pathogenic resident microbiota, leading to an elevated inflammatory response [5].

In IBD patients, not only the quantity of commensal bacteria reduced but also the quality of microbiota composition is altered, with reduction of *Firmicutes* and *Bacteroidetes*. As a consequence of the dysbiosis, the relative abundance of *Enterobacteriacae* is increased in IBD patients compared to healthy controls, although their absolute numbers remained unaltered [26]. There are findings which present decreased clostridia concentrations accompanied by a decrease in *Bacteroides* [14]. Apart from that data in several studies were revealed aberrancies in *Bifidobacterium* populations with significant reductions of the counts and bacterial diversity of *Lactobacilli* in IBD patients compared to healthy individuals.

It is known that commensal flora in infant intestine is rich in Bifidobacteria, Lactobacilli and with other protective components provide a reduction in colonization with potential pathogens. Alterations in the microbial intestinal balance may result in subsequent pathologic disorders like functional or chronic inflammatory diseases of the intestinal tract [8].

In children both mucosal immune system and intestinal flora are still in the developmental stage. Taken together it appears that IBD in infants represent a specific group of patients with particular gene defects, phenotypic appearance, and intestinal immunopathology that differs from older children and adults [28].

Therefore, the study of intestinal mucosal barrier and immune disorders, as well as alterations in the microbial intestinal balance is of particular interest in infant IBD.

The main goal of therapy for IBD is to cure pathology or at least induce a clinical remission and then maintain it for a long period of time. Conventional therapy does not always provide efficient results, indicating that a considerable need for develop new and more effective therapy is required.

Dietary management of IBD may be an interesting alternative to drug therapy if it proves to be effective without side effects and can be used as a remission induction and maintenance therapy [1]. Nutrients may be involved in the modulation of the immune response, thus, as components of cell membranes, nutrients can mediate the expression of proteins involved in the immune response, such as cytokines, adhesion molecules, etc.[12,13].

It has been studied the effects of the micronutrients, probiotics, prebiotics and n-3 long chain polyunsaturated fatty acids (n-3 LC PUFA) to modulate host defense mechanisms, to develop normal digestive function, to protect from bacterial translocation, and to preserve mucosal barrier integrity in infants. Nowadays probiotics, prebiotics and n-3 long chain polyunsaturated fatty acids refer to functional food («...food that contains known biologically-active compounds which when in defined quantitative and qualitative amounts provides a clinically proven and documented health benefit, and thus, an important source in the prevention, management and treatment of diseases») [20] .

Recently, probiotics, prebiotics and n-3 LC PUFA were found to have a potential relationship with IBD pathophysiology and thus can be efficient in IBD treatment in infants. So far few studied were perform to research the role of these nutrients in treatment of IBD in infants.

Probiotics upon ingestion in specific numbers have beneficial effect and exert their therapeutic effects to modulate the barrier function, the inhibition of pathogenic bacteria, the intestinal production of cytokines, with anti-inflammatory properties and enhancement of the digestion and absorption of food There is a great deal of evidence documenting the immunemodulatory ability of probiotic bacteria; at the same time, the efficiency of probiotics is not enough while ingested alone in the course of treatment either intestinal dysbiosis or intestinal diseases accompanied by microbial imbalance [23,24]. It is therefore reasonable to suggest the beneficial effects of the symbiotic formulations of probiotics with prebiotics.

Prebiotics include oligo- and polisaccharides which, owing to their chemical structure are indigestible in the small intestine and are anaerobically fermented by bacteria in the colon. This fermentation of non-digestible dietary carbohydrate results in the production of short chain fatty acids, (acetate, proprionate, butyrate), that have significant positive impacts as an energy source on intestinal epithelial cell function. The result is the restoration of the metabolic function of the intestinal cells that accelerate the intestinal repair preserving the integrity of the intestinal mucosa and downregulating the exacerbated immune response presented in IBD [4].

Prebiotics also contribute to restoration of intestinal mucosal barrier supplying epithelial cell with carbohydrate compounds which are used in synthesis of mucins [9]. Therefore, the prebiotics are indispensable to support and protect intestinal tract mucosa and so to reduce the incidence of intestinal lesions, including intestinal inflammation.

Other important substrates in modulating the immune response are dietary lipids. The composition of lipids in the cell membrane is modified by dietary changes and can influence cellular responses. The decrease of n-3 LC PUFA, which increases the n-6/n-3 LC PUFA ratio leads to a predominance of proinflammatory eicosanoids, i.e. the development of pro-

inflammatory background in the body. At the same time, n-3 LC PUFA have beneficial effect by competing with n-6 LC PUFA for the production of lipid inflammatory mediators such as eicosanoids and cytokines[16]. As structural substrates of epithelial membrane the consumption of n-3 LC PUFA can positively influence the function of intestinal epithelium cells, improve mucosal adhesion sites for gastrointestinal bacteria and as a result, the dietary n-3 PUFA could modulate the probiotics action.

Present data suggest that the combination of conventional therapy with simultaneous involvement of such immunoinutrients like probiotics, prebiotics and n-3 LC PUFA would improve the results of the treatment associated with restoration of microbial homoeostasis in the gut, down-regulate intestinal inflammation and ameliorate the diseases.

The objective of our study was to assess the effectiveness of simultaneous application of immunonutrients (probiotics, prebiotics and n-3 LC PUFAs) in the treatment of inflammatory bowel diseases in infants.

Patients and methods

The study was a randomized controlled clinical trial of children with chronic non-specific non-ulcerative colitis (CNNC) consecutively enrolled over 6 month period at the Department of Nutritional Problems and Somatic Diseases in Infants of the SI «Institute of Pediatrics, Obstetrics and Gynecology of National Academy of Medical Science of Ukraine». The diagnosis was established on accepted historical, clinical, laboratory and imaging criteria by the «Standardized protocols of medical care for children with digestive tract disease» approved by Ministry of Health of Ukraine.

A total of 92 children (mean age 1.6 years, range 1–3 years, female/male 10/13) were enrolled into the study: all patients had a confirmed endoscopic diagnosis of CNNC. Disease activity was assessed by the Disease Activity Index (DAI). The latter is calculated by summing the scores of four variables each of which is graded on a scale from 0 to 3: stool frequency, abdominal pain/cramps, physician's assessment of disease activity and mucosal appearance. The maximum potential score is 12.

Infectious and immunological diseases as well as malabsorption syndromes and food allergy were excluded in all. At admission, all patients were checked for complaints, family and health history, symptom onset, diseases manifestation. Physical examination was performed and the plan for laboratory tests and imaging examination was designed. Laboratory tests included evaluation of complete blood count (CBC), stool specimens for culture and microscopic examination, blood chemistry and immunological investigations. Endoscopy was performed prior to the trial.

Clinical evaluation of children was performed during their staying at the department until the discharge. The control visit was performed after 3 and 6 months

Recruited children eligible to participate to this study were randomly divided in two groups, 50 children were assigned to receive immunonutrients (main group) which they consumed during 3 months on daily base, and other 42 children were control group. All children received conventional therapy which included aminosalicylates with concomitant symptomatic treatment, in severe cases additionally steroids. For each individual patient exclusively were made decisions regarding therapeutic interventions corresponded to protocol recommendations.

Micronutirents used in our trial were probiotics, prebiotics and n-3 LC PUFA. Probiotics were provided by probiotic preparation consisted of viable non-lyophilized bacteria of two strains of *Bifidobacterium* (*B. bifidum, B. longum*), three strains of *Lactobacillus* (*L. Acidophilus, L. Delbrueckii ssp. Bulgaricus, L. Helveticus*), *Propionibacterium* (*P.Freudenreichii ssp. Shermanii*, *P.Acidipropionici*), *Lactococcus Lactis*, *Streptococcus* (S.Salivarius spp. Thermophilus). The concentration of bacteria in probiotic preparation (KOE/ml) were not less than: *Bifidobacteria* — $1{,}0x10^8$, *Lactobacilli* and *Lactococci* — $1{,}0x10^9$, *Propionibacteria* — $3{,}0x10^7$.

Prebiotics used were inulin-type prebiotics that contain fructans. Fructans are a category of nutritional compounds comprised of oligo- and polysaccharides extracted from chicory root. At present, inulin is commercially available as a nutritional supplement or used in infants formulas. In our research inulun had been used in daily dose of 4 g.

All children of main group additionally consumed nutritional supplement of n-3 LC PUFA consisted of docosahexaenoic and eicosapentaenoic acids in daily dose of 150 mg and 100 mg respectively.

In order to assess the effectiveness of immunonutrients in IBD treatment, apart from clinical evaluation in our study we investigated immunological disorders assessing expresson of serum tumour necrosis factor alpha (TNF-α) that play an important role in pathogenesis of IBD as well as different pro-and anti-inflammatory interleukins. Enzyme-Immuno-Sorbent-Assay method (ELISA) was used. In this trial there was also evaluated microflora disbalance determining the quantitative status of indigenous bacteria (*Bifidobacteria, Lactobacilli*) at rectal level. Bacteriological analysis was performed in accordance with current conventional methods.

Mean and median values were calculated for dimensional variables after controlling for normality of distribution. Were used parametric and nonparametric statistic methods. The Student's t-test for normally distributed variables and the χ^2 and Fisher's exact tests for categorical variables were used where appropriate. Survival analysis was used to analyze the data set with respect to relapse. Data were also correlated by Pearson's correlation coefficient, and 95% confidence intervals were calculated. Statistical analysis was performed using Exsell statistical software package for Windows.

Results

A total of 98 patients with diagnosed CNNC were screened. Six subjects were excluded, because the parents refused to follow study. Ninty-two children were eligible and participated to this study. Of them, 50 were randomly assigned to receive immunonutrints (main group), the rest children composed the control group. Demographic data for the study groups were well matched with respect to age, sex, extension of colitis, and duration of symptoms at onset.

Linear growth and weight at diagnosis were normal in all children. No significant differences in weight or height at diagnosis and during follow-up were observed between compared groups.

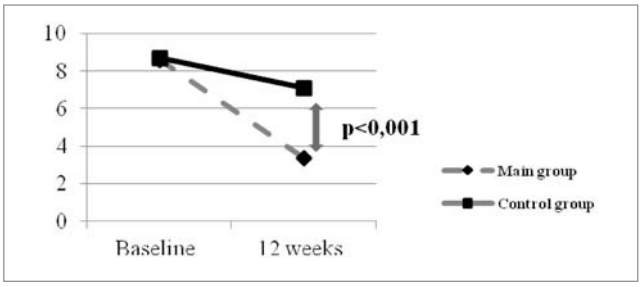

Fig. 1. Mean values of Disease Activity Index score at baseline and after 12 weeks of the trial in the two study groups (92 patients)

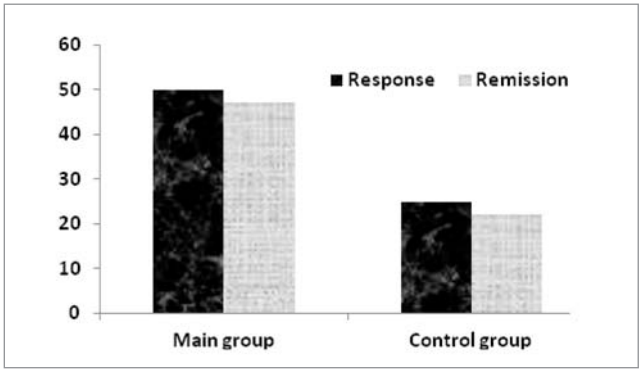

Fig. 2. Clinical outcome of treatment in infants with NCCN (number of patients)

During the course of the study, consumption of immunonutrients was well tolerated and no cases of disease deterioriation or serious adverse events were reported. At baseline, all patients had a moderate active CNNC and the two groups were comparable for the DAI. Summarising the results of study, during follow-up DAI score decreased significantly in the main group (3.4±1.2 versus baseline 8.6±0.8, P < 0.01) compared to control group (7.1±1.1 versus baseline 8.7±0.7, P > 0.05).

All patients of the main group and 25 of 42 (59,5 %) infants of control group had a clinical response (P < 0.05), whereas remission was reached in 47 of 50 (95 %) infants of the main group and in 22 of 42 (52,4 %) infants of control group (P < 0.05) (Fig. 2).

In our study we investigated mucosa-associated bacteria which belong to commensal anaerobes such as *Bifidobacteria* and *Lactobacilli*. We found a significant reduction in the number of these bacteria in all NCCN patients. At baseline, the level of *Bifidobacteria* was 5,7±0,3 KOE/l (normal level — 9,1±0,7 KOE/l) and the level of Lactobacilli was 4,9±0,3 KOE/L (normal level — 8,4±0,8 KOE/L).

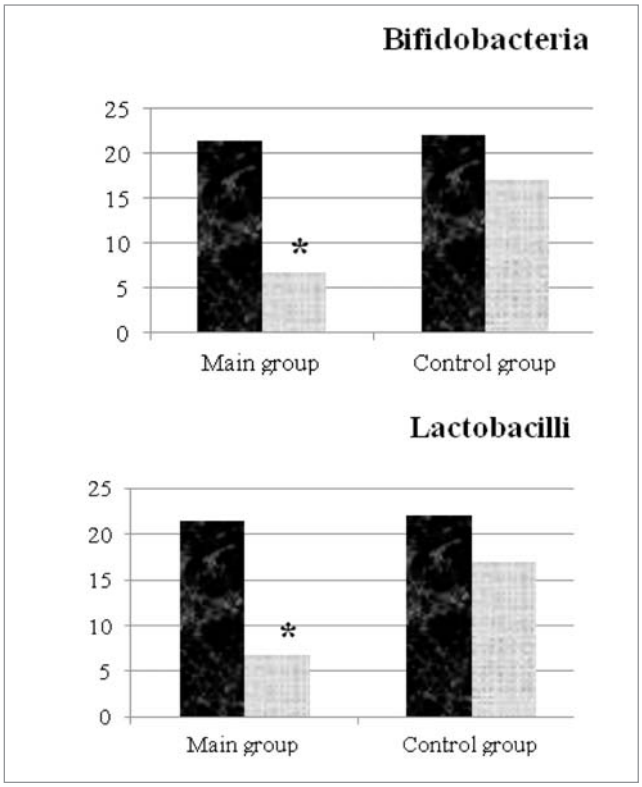

Fig. 3. Differences in the number of cultured intestinal bacteria between study groups, at baseline and after 12 weeks of treatment (KOE/L), * — p<0,05

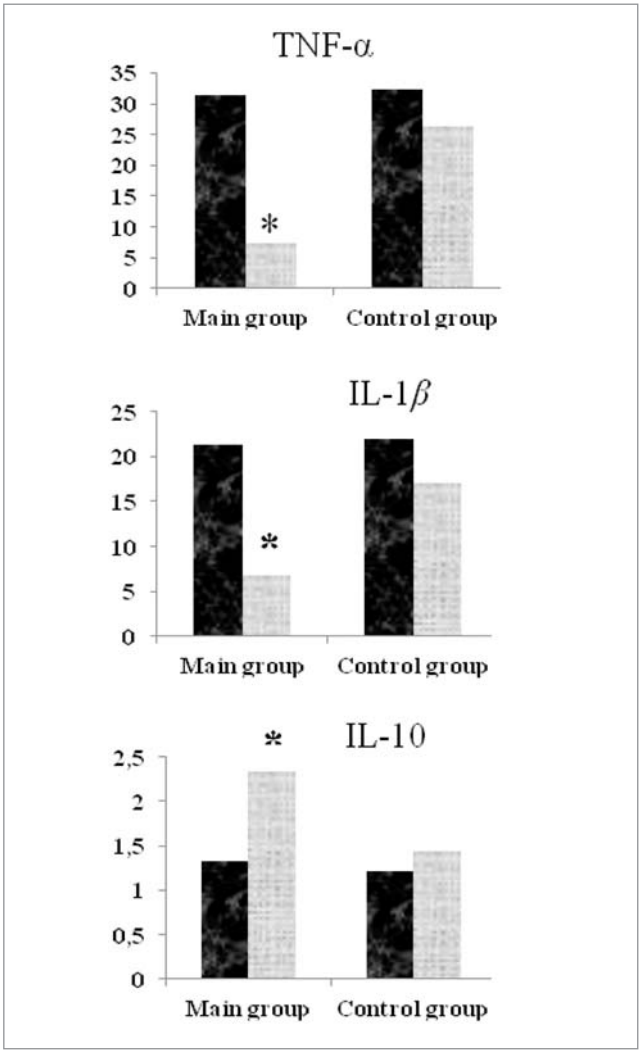

Fig. 4. Differences in expression levels of serum cytokines between study groups, at baseline and after 12 weeks of treatment (pg/ml), * — p<0,001

After treatment the total numbers of cultured intestinal bacteria was increased mostly in the patients of the main group. The analysis showed statistically significant rise both *Bifidobacteria* and *Lactobacillii* in the samples of intestinal cultures (p<0,05). In control group only a tendency was observed in increasing the number of this microflora, however, not statistically significant (Fig. 3).

The differences in serum cytokine levels in the two groups were not significant before treatment. At the post-trial evaluation there was a significant increase in the expression levels of IL-10 and a significant decrease in those of IL-1b, TNF-a expression levels only in the main group (P < 0.01) which means that the positive immunological changes in serum cytokines profile was noted (Fig.4).

Compliance with the immunonutrient application in both groups was satisfied. No side effects or significant changes from baseline values in any of the laboratory parameters examined, attributable to treatment with either immunonutrients or without, were registered.

Discussion

In children of first years of life there are differences in clinical features of IBD compared to elder children and adults.

Typical manifestation of the chronic colitis in infants is characterized by mucosal inflammation limited to distal part of the colon (proctosigmoidit). Considering that this part of intestine is colonized by a huge number of intestinal bacteria, microbial imbalance, in other words, a breakdown in the balance between «protective» and «harmful» intestinal bacteria, can promote inflammation. In infants the concept of dysbiosis disorders in development of IBD is most acceptable because intesninal microbiota in this age is still in developing stage as well as mucosal immune system. Taken together it appears that pediatric IBD represent a specific group of patients.

As the microbial environment has been shown to play a role in the development of IBD, targeting of the microbiota presents an option for therapeutic intervention. In this way, manipulating the abnormal enteric microbiota to decrease pathogenic or potential pathogenic species and enhancing the concentration and metabolic activity of the benecial species has tremendous potential for therapeutic benefit.

The indication for probiotics in IBD is grounded on a number of human and animal studies indicating that the enteric flora is centrally involved in the pathogenesis of chronic intestinal inflammatory diseases. Their clinical usefulness and safety have been documented in different clinical trials showing efficacy in reducing incidence and severity of diarrhoea of different cause as well as in improving the course of gastrointestinal functional disorders in childhood [11, 17.]. Studies have documented the ability of probiotics to colonise upper and lower intestinal mucosa as well as to modulate intestinal immunological response [2]. In the last years, several studies have shown a beneficial effect of different probiotic preparations in inducing and maintaining remission in adults and children with IBD [7, 29]. In contrast to mentioned studies, other meta-analysis concluded that there was no evidence that probiotics were superior to placebo or aminosalicylates for the induction of remission and that the use of probiotics as induction therapy for UC could not be recommended [22].

Discrepancy in the opinions of positive or ineffective action of probiotics is the results of the unresolved issues (dose, duration of use, single or multistrain formulation, etc.) which require further detailed investigation, randomized controlled clinical trials. In our opinion, the use of probiotics alone in different pathologic conditions of the digestive tract or intestinal diseases should be supported by other nutrients. Synergistic action of such nutrients as probiotics, prebiotics and n-3 LC PUFS can significantly improve the functional status of intestinal tract in different level: microflora balance, mucosal protective barrier, epithelicytes and their integrity. Furthermore, we hypothesize that the success of our treatment may be related to the use of a probiotic preparation (multiprobiotics) rather than one prodiotic [15,18].

This randomized controlled clinical study in children with chronic non-specific non-ulcerative colitis provides evidence that protracted intestinal inflammation can be reduced by administration of probiotics, prebiotics and n-3 LC PUFA in addition to conventional therapy.

At baseline, the results of our study showed significant reductions of the *Bifidobacteria* and *Lactobacillii* counts in the samples of intestinal culturesg. These bacteria represent indigenous bacteria that are predominant strains in infantile intestine. Such changes indicate that in infants with IBD microbiota composition is altered with possible increase pathogens and/or potential pathogenic bacteria. Abnormal colonization of the intestinal mucosa induces the release of high amounts of proinflamatory interleukins, particulary, TNF-α, at the same time inhibition of anti-inflammatory cytokines takes place [15]. According to our study such alterations were strongly associated with chronic non-specific non-ulcerative colitis activity.

It was noticeable that in our trial clinical efficacy of the consumption of immunonutrient complex was accompanied by a significant improvement of intestinal mucosa as documented by endoscopy and that there were striking changes in the expression of cytokines known as important immune factors in the mechanisms leading to IBD. Support for a favorable action of immunonutrients in infants suffering from CNNC is proved by positive quantitative changes of indigenous bacteria (*Bifidobacteria* and *Lactobacilli*).

Many years there were used classical bacteriological methods to study intestinal microorganisms. Recently, molecular genetic technologies radically changed our understanding of the composition of microflora in the gut. But despite of the fact that bacteriological methods carried out to study intestinal microbiota not fully reflect the complexity of the content of the intestinal microflora, it includes most common bacteria encountered in infantile intestine. Hence, intestinal bacteriological analysis still is adequate to assess the composition of intestinal microflora especially in infants.

The results of the study document the efficacy of application of immunonutrients (probiotics, prebiotics and n-3 LC PUFAs) as an accompanying treatment in improving mucosal inflammation and redusing disease activity in infants with chronic nonspecific non-ulcarative colitis as well as positive changing in the expression levels of pro- and anti-inflammatory cytokines. At the same time immunonutrients actins as symbiotics contribute to the improvement of intestinal microflora status.

This randomized clinical trial demonstrated favorable role of immuninutrients to ameliorate clinical manifestation of the disease and maintain remission in infants suffering from chronic inflammatory bowel desease.

On the basis of our results, simultaneous consumption of multiprobiotics, prebiotics and n-3 LC PUFA as natural, safe, and well-tolerated, adjunctive treatment to conventional therapy may provide a simple and attractive way to treat pediatric IBD. Further well designed randomized controlled trials, however, with higher patient numbers may be justified to confirm results of current pediatric study and future research may allow elucidating the mechanisms underlying the actions of immunonutrient supplementation on IBD.

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REFERENCES

1. Albenberg L.G. Food and the gut microbiota in inflammatory bowel diseases: a critical connection / Albenberg L.G., Lewis J.D., Wu G.D. // Curr. Opin. Gastroenterol. — 2012. — Vol.28,№4. — P.314 — 320.
2. Bezirtzoglou E. Immunology and probiotic impact of the newborn and young children intestinal microflora / E. Bezirtzoglou, E. Stavropoulou // Anaerobe. — 2011. — Vol.17,№6. — P.369 — 374.
3. Chemical and cytokine features of innate immunity characterize serum and tissue profiles in inflammatory bowel disease / C.G. Knutson, A. Mangerich, Y. Zeng [et al.] Proc. Natl. Acad. Sci. USA. — 2013. — Vol.110,№26. — P.2332 — 2341.
4. Corazziari E. S. Intestinal Mucus Barrier in Normal and Inflamed Colon / E. S. Corazziari // J. Pediatric Gastroenterology and Nutrition. — 2009. — Vol.48. — P.54 — 55.
5. Fava F. Intestinal microbiota in inflammatory bowel disease: Friend of foe? / F. Fava, S. Danese // World J. Gastroenterol. — 2011. — Vol.17,№5. — P.557 — 566.
6. Fiocchi C. IBD: advances in pathogenesis, complications, diagnosis, and therapy / C. Fiocchi // Curr Opin Gastroenterol. — 2012. — Vol.28, №4. — P.297 — 300.
7. Guandalini S. Update on the role of probiotics in the therapy of pediatric inflammatory bowel disease / S. Guandalini // Expert. Rev. Clin. Immunol. — 2010. — Vol.6,№1. — P.47 — 54.
8. Guarner F. The intestinal microbiota and inflammatory bowel disease / F.Guarner // Gastroenterol. Hepatol. — 2011. — Vol.34,№3. — P.147 — 154.
9. Horvath A. Probiotics, prebiotics, and dietary fiber in the management of functional gastrointestinal disorders / A. Horvath, H. Szajewska // World Rev. Nutr. Diet. — 2013. — Vol.108:40 — 48.
10. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review / Molodecky N.A., Soon I.S., Rabi D.M. [et al.] / Gastroenterology. — 2012. — Vol.142,№1. P.46 — 54.
11. Indrio F, Riezzo G, Raimondi F, et al. The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal motility in preterm newborns. J Pediatr 2008; 152: 801 — 806.
12. Intestinal mucosal defense system, Part 1. Consensus recommendations for immunonutrients. [J. Neu, W.A. Mihatsch, J. Zegarra [et al.] // J. Pediatr. — 2013. — Vol.162,№3(Suppl). — P.56 — 63.
13. Intestinal mucosal defense system, Part 2. Probiotics and prebiotics / T. Murguia-Peniche, W.A. Mihatsch, J. Zegarra [et al.] // J. Pediatr.-2013. — Vol.162,№3 (Suppl). — P.64 — 71.
14. Macfarlane S. Intestinal bacteria and inflammatory bowel disease / S. Macfarlane, H. Steed, G. T. Macfarlane // Critical Reviews in Clinical Laboratory Sciences. — 2009. — Vol.46,№1. — P.25 — 54.
15. Magrone T. The interplay between the gut immune system and microbiota in health and disease: nutraceutical intervention for restoring intestinal homeostasis / Magrone T., Jirillo E. // Curr. Pharm. Des. — 2013. — Vol.19, №7. — P.1329 — 1342.
16. Mills S.C. The potential interactions between polyunsaturated fatty acids and colonic inflammatory processes / S.C. Mills, A.C. Windsor, S.C. Knight // Clin. Exp. Immunol. — 2005. — Vol.142,№2. — P.216 — 228.
17. Miniello VL, Brunetti L, Tesse R, et al. Lactobacillus reuteri modulates cytokines production in exhaled breath condensate of children with atopic dermatitis. J Pediatr Gastroenterol Nutr 2010; 50: 573 — 6. 29.
18. Nutritional protective mechanisms against gut inflammation / Viladomiu M., Hontecillas R., Yuan L. [et al.] // J. Nutr. Biochem. — 2013. — Vol.24,№6. — P.929 — 939.
19. Ohland C.L. Probiotic bacteria and intestinal epithelial barrier function / C.L. Ohland, W.K. Macnaughton // Am. J. Physiol. Gastrointest. Liver Physiol. — 2010. — Vol.298,№6. — P.807 — 819.
20. Ozen A. E. Worldwide consumption of functional foods: a systematic review / A. E. Ozen, A. Pons, J. A. Tur // Nutrition Reviews. — 2012. — Vol.70,№8. — P.472 — 481.
21. Ponder A. A clinical review of recent findings in the epidemiology of inflammatory bowel disease / Ponder A., Long M.D. // Clin. Epidemiol. — 2013. — Vol.25,№5. — P.237 — 247.
22. Probiotics for maintenance of remission in ulcerative colitis / K.Naidoo, K.Naidoo, M. Gordon [et al.] // Cochrane Database Syst. Rev. — 2011. — Vol.12. — P.1 — 22.
23. Probiotics, prebiotics and immunomodulation of gut mucosal defences: homeostasis and immunopathology / Hardy H., Harris J., Lyon E. [et al.] // Nutrients. 2013. — Vol.5,№6. — P.1869 — 1912.
24. Quah S.H. Role of probiotics and nutrition in the management of chronic inflammatory bowel disease in children / S.H.Quah // Singapore Med.J. — 2013. — Vol.54,№4. — P.183 — 184.
25. Rescigno M. Mucosal immunology and bacterial handling in the intestine / M.Rescigno // Best Pract.-Res. — Clin. — Gastroenterol. — 2013. — Vol.27,№1. — P.17 — 24.
26. Shim J.O. Gut Microbiota in Inflammatory Bowel Disease / J.O. Shim // Pediatr. Gastroenterol. Hepatol. Nutr. — 2013. — Vol.16,№1. — №17 — 21.
27. Taschuk R. Commensal microbiome effects on mucosal immune system development in the ruminant gastrointestinal tract / Taschuk R., Griebel P.J. // Anim. Health Res. Rev. — 2012. — Vol.13,№1. — P.129 — 141.
28. Transcriptional activity of the dominant gut mucosal microbiota in chronic inflammatory bowel disease patients / Rehman A., Lepage P., Nolte A.[et al.] // J. Med. Microbiol. — 2010. — Vol.59. — P.1114 — 1122
29. Wang Z.H. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy / Z.H. Wang, Q.Y. Gao, J.Y. Fang // J. Clin. Gastroenterol. — 2013 Vol.47(1):25 — 32.
30. Xavier R.J. Unravelling the pathogenesis of inflammatory bowel disease // R.J. Xavier, D.K. Podolsky // Nature. — 2007. — Vol.448. — P.427 — 434.

РАНДОМИЗИРОВАННЫЕ КЛИНИЧЕСКИЕ ИССЛЕДОВАНИЯ: ЭФФЕКТИВНОСТЬ ИММУНОНУТРИЕНТОВ В ТЕРАПИИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ КИШЕЧНИКА У ДЕТЕЙ РАННЕГО ВОЗРАСТА

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В настоящее время рассматриваются новые подходы в лечении хронических воспалительных заболеваний кишечника (ХВЗК) у детей. Такие подходы предполагают организацию рациональной терапии с учетом влияния на патофизиологические механизмы и обеспечения безопасности терапевтических мероприятий. На сегодня установлено влияние таких иммуннонутриентов, как пробиотики, пребиотики и омега-3 полиненасыщенные жирные кислоты на патогенетические механизмы развития хронических воспалительных заболеваний кишечника. Предполагается, что комплексное использование в терапии ХВЗК этих нутриентов может усилить терапевтический эффект, а именно, способствовать снижению активности воспаления и усилению репаративных процессов в слизистой кишечника, тем самым, достижению более благоприятного течения, выздоровления или стойкой ремиссии ХВЗК у детей раннего возраста. До настоящего времени данные о таких исследованиях в современной литературе практически отсутствуют.

Целью настоящей работы была оценка эффективности комплексного применения иммуннонутриентов (пробиотики, пребиотики и омега-3 длинноцепочечные полиненасыщенные жирные кислоты) в лечении хронического неспецифического неязвенного колита у детей раннего возраста.

Методы: Обследовано 92 ребенка (средний возраст 1,6 лет, возрастной интервал 1-3 года, девочки/мальчики 10/13) с хроническим неспецифическим неязвенным колитом (ХННК). Все дети получали общепринятую терапию. Методом рандомизации определены две группы: 50 детей (основная группа) наряду с общепринятой терапией получали иммуннонутриенты, 42 ребенка составили контрольную группу. Клинико-лабораторные и инструментальные методы исследования, а также оценку экспрессии интерлейкинов и микробиологический анализ микрофлоры кишечника (бифидо- и лактобациллы) проводили в начале и конце наблюдения. Для оценки эффективности терапии и особенностей течения заболевания рассчитывался индекс активности ХННК.

Результаты: Проведенные исследования показали, что индекс активности ХННК у детей основной группы в динамике уменьшился с 8,6±0,8 до 3,4±1,2 ($p<0,01$), в то время как у детей контрольной группы этот показатель в динамике наблюдения достоверно не изменялся (8,7±0,7 и 7,1±1,1, $p>0,05$). Все пациенты основной группы и 25 из 42 (59,5%) детей контрольной группы имели улучшение клинического течения заболевания, ремиссия была достигнута у 47 из 50 (95,0%) детей основной группы, в то время как у детей контрольной группы у 22 из 42 (52,4%). В динамике исследования у детей основной группы отмечалось значительное улучшение состояния индигенной микрофлоры кишечника наряду с выраженными положительными изменениями профиля интерлейкинов. В обеих группах обострений ХННК, а также побочных эффектов использования иммуннонутриентов не отмечалось.

Выводы: Данные исследования показали, что применение пробиотиков и пребиотики в комбинации с омега-3 длинноцепочечными полиненасыщенными жирными кислотами в комплексной терапии хронического неспецифического неязвенного колита способствует значительному улучшению клинического течения заболевания, что связано со снижением воспалительных изменений в слизистой и уменьшением активности заболевания, значительным улучшением показателей иммунной системы и состояния микрофлоры кишечника. Показана эффективность иммунонутриентов в восстановлении слизистой и поддержании ремиссии при хроническом воспалительном процессе в кишечнике.

Ключевые слова: хронический неспецифический неязвенный колит, дети раннего возраста, иммуннонутриенты.

РАНДОМІЗОВАНІ КЛІНІЧНІ ДОСЛІДЖЕННЯ: ЕФЕКТИВНІСТЬ ІММУНОНУТРІЄНТОВ У ТЕРАПІЇ ХРОНІЧНИХ ЗАХВОРЮВАНЬ КИШЕЧНИКУ У ДІТЕЙ РАННЬОГО ВІКУ

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На сьогодні розглядаються нові підходи в лікуванні хронічних запальних захворювань кишечника (ХВЗК) у дітей. Такі підходи передбачають організацію раціональної терапії з урахуванням впливу на патофізіологічні механізми та забезпечення безпеки терапевтичних заходів. Встановлено вплив таких іммуннонутрієнтів, як пробіотики, пребіотики та омега-3 довголанцюгові поліненасичені жирні кислоти на патогенетичні механізми розвитку хронічних запальних захворювань кишечника. Припускається, що комплексне використання в терапії ХВЗК цих нутрієнтів може посилити терапевтичний ефект, а саме, сприяти зниженню активності запалення і посиленню репаративних процесів у слизовій кишечника, тим самим, досягненню більш сприятливого перебігу, одужання або стійкої ремісії ХВЗК у дітей раннього віку. До теперішнього часу дані про такі дослідження в сучасній літературі практично відсутні.

Метою цієї роботи була оцінка ефективності комплексного застосування іммуннонутрієнтов (пробіотики, пребіотики та омега-3 довголанцюгові поліненасичені жирні кислоти) в лікуванні хронічного неспецифічного невиразкового коліту у дітей раннього віку.

Методи: Обстежено 92 дитини (середній вік 1,6 років, віковий інтервал 1-3 роки, дівчатка/хлопчики 10/13) з хронічним неспецифічним невиразковий колітом (ХННК). Всі діти отримували загальноприйняту терапію. Методом рандомізації визначено дві групи: 50 дітей (основна група) поряд із загальноприйнятою терапією отримували іммуннонутрієнти, 42 дитини склали контрольну групу. Клініко-лабораторні та інструментальні методи дослідження, а також оцінку експресії інтерлейкінів та мікробіологічний аналіз мікрофлори кишечника (біфідо- і лактобацили) проводили на початку і наприкінці спостереження. Для оцінки ефективності терапії та особливостей перебігу захворювання розраховувався індекс активності ХННК.

Результати: Проведені дослідження показали, що індекс активності ХННК у дітей основної групи в динаміці зменшився з 8,6±0,8 до 3,4±1,2 ($p<0,01$), у той час як у дітей контрольної групи цей показник в динаміці спостереження достовірно не змінювався (8,7±0,7 і 7,1±1,1, $p>0,05$). Всі пацієнти основної групи і 25 з 42 (59,5%) дітей контрольної групи мали поліпшення клінічного перебігу захворювання , ремісія була досягнута у 47 з 50 (95,0%) дітей основної групи , в той час як у дітей контрольної групи у 22 з 42 (52,4%). У динаміці дослідження у дітей основної групи відзначалося значне поліпшення стану індігенной мікрофлори кишечника поряд з вираженими позитивними зміни профілю інтерлейкінів. В обох групах загострень ХННК, а також побічних ефектів використання іммуннонутрієнтов не відзначалося.

Висновки: Дані дослідження показали, що застосування пробіотиків і пребіотики в комбінації з омега-3 довголанцюговими поліненасиченими жирними кислотами в комплексній терапії хронічного неспецифічного невиразкового коліту сприяє значному поліпшенню клінічного перебігу захворювання, що пов'язано зі зниженням запальних змін в слизовій та зменшенням активності захворювання, значним поліпшенням показників імунної системи та стану мікрофлори кишечника. Показана ефективність іммунонутрієнтов у відновленні слизової і підтримці ремісії при хронічному запальному процесі в кишечнику.

Ключові слова: хронічний неспецифічний невиразковий коліт, діти раннього віку, іммуннонутрієнти.

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