Serum immunoglobulin levels in children with respiratory infections who used a synbiotic dietary supplement

Nivo imunoglobulina u serumu u dece obolele od respiratornih infekcija i lečene sinbiotikom

Fanika Pantović

Fanika Pantovic

Dom zdravlja "Danica i Kosta Šamanović", Knić

Health Center "Danica i Kosta Samanovic", Knic, Serbia

PRIMLJEN 30.06.2012.

RECEIVED 30.06.2012.

PRIHVAĆEN 22.02.2013.

ACCEPTED 22.02.2013.

SAŽETAK

Cilj. Cilj ovog istraživanja je da se ispita efikasnost i optimalno vreme suplementacije sinbiotikom u atopične dece obolele od respiratorne i/ili infekcije uha.

Metode. Istraživanjem subila obuhvaćena hospitalizovana deca zbog učestalih respiratornih infekcija i/ili inflamacije uha, u kojih smo analizirali nivo imunoglobulina pre i posle lečenja, ponavljanim merenjima.

Rezultati. Hospitalizovana deca su prosečnog uzrasta 19 meseci, svi su imali deficit IgA, 58% je pokazalo deficit IgG, 81% su atopičari i u isto vreme, boluju od respiratornih infekcija (pneumonija 45%, infekcija srednjeg uha 26%, faringitis 74%) i pratećih bolesti (malokrvnost 26%, povećanje adenoidima 6%, ekcema 13%, šištanje-bronhitis 16%, astma 42%, urtikarija 3%). Posle 3 meseca lečenja sinbiotikom nivo IgA je porastao za 1.8 puta od 0.33 ± 3.42 g/l ($p < 0.05$) do prosečne vrednosti 0.6 ± 0.78 g/l u 35% dece i nakon 6 meseci utvrđen je porast za 3.9 puta do prosečne vrednosti 1.3 ± 1.76 g/L u 81% dece ($t=0.43$, $p < 0.05$).

Zaključak. Optimalna dužina primene sinbiotika, dok se ne smanji rizik od čestih respiratornih infekcija kod male dece atopičara, je najmanje 6 meseci, mada se kliničko poboljšanje postiže za 3 meseca.

Ključne reči: probiotici; sinbiotici; imunoglobulini; deca; infekcija.

ABSTRACT

Objective. The purpose of this study was to investigate the effectiveness and the optimal time of supplementation with synbiotic in atopic children with common respiratory and/or ear infections.

Methods. We recruited inpatients children with frequent respiratory infections and/or inflammation of the ear and analyzed pretreatment and post-treatment level of immunoglobulins using repeated measures analysis.

Results. Hospitalized children are old averaging 19 months, all had deficiency of IgA, 58% showed deficiency of IgG, 81% are the atopics and at the same time, suffer from respiratory infection (pneumonia 45%, middle ear infection 26%, pharyngitis 74%) and concomitant diseases (anemia 26%, enlarge adenoids 6%, eczema 13%, wheezing bronchitis 16%, asthma 42%, urticaria 3%). After 3 months treatment by synbiotic level of IgA increased for 1.8 times up from 0.33 ± 3.42 g/l to 0.6 ± 0.78 in 35% children and after 6 months increased for 3.9 times up to 1.3 ± 1.76 in 81% children ($t=0.43$, $p < 0.05$).

Conclusion. Optimal duration of supplementation with synbiotic to reduce the risk of common infectious disease, in young, atopic children, is at least 6 months although achieved clinical improvement after 3 months.

Key words: probiotics; synbiotics; immunoglobulins; child; infection.

KORESPONDENCIJA / CORRESPONDENCE

Dr Fanika Pantović, Dom zdravlja "Danica i Kosta Šamanović", 34240 Knić, Tel: 0628035192, E-mail: ppantoviczastava@gmail.com

Fanika Pantović, MD, Health Center "Danica i Kosta Samanovic", 34240 Knic, Serbia, Phone: +381628035192, E-mail: ppantoviczastava@gmail.com

INTRODUCTION

Probiotics are living microorganisms that favorable act at human health. Favorable act of probiotic is emphasized by prebiotic in synbiotic⁽¹⁾. Together they modulate mucosal and systemic immunity and improve nutritive and microbiota balance in an intestinal tract.² During the same time probiotics inhibits proliferation of pathogenic bacteria and can help prevention of pathogenic infections.^{3,4} Probiotic causes an initial mild enteral inflammation which activates dendritic cells to stimulate NK-cells and macrophages and the end protects against infection. Bifidobacteria (BifB.) from probiotics increase levels of anti-inflammatory cytokine IL10 and IFN-gamma and immunoglobulins G, A and M and decrease levels of IL-4 and pro-inflammatory cytokines (IL-1beta, IL-6, TNF-alpha, IL-8, NFkB, IL-12) and immunoglobulin E.^{5,6,7}

Actually, BifB and lactobacillus rhamnosus GG (LGG) from probiotic immunomodulation seems with inhibition of immunoglobulin E(IgE) production. Probiotic makes immunomodulation and establishes mucosal tolerance that means inhibition of toll-like receptors 3 and 1, CD4, CD25, then high expression of toll-like receptors 2 and 9, CD83, development of tolerogenic dendritic cells and increasing of level of TGF-beta and IL-10 and PGE2.⁸ Also, probiotics contribute to maturing gut barrier and rise level of calprotectin and alpha-1-atitrypsin.^{9,10,11} BifB stimulate production of IL-10 and expression of CD83 that both inhibit releasing of Th2 cells cytokines.

At birth, baby has production of BifB and low level of Lactobacilli opposite lot of E.coli and Enterococci what got average fecal pH 6. Very soon fecal pH falls at 4,5-5 because very fast production of Bacteroides, Peptococcus and Clostridium. In adult and elderly level of BifB falls and level of Clostridia rises that made increased of faecal pH to 6-7,5. During immunity answer to infective agent first increase level of IL-2, INF-gama and IL-8.

In fetus with atopic heredity we can find prenatal proliferation of mononuclear cells to houst dust mites, activity of toll-like receptors is low and we find low level of IL-6 but high level of IFN-gamma that contribute developing of pre-existing inflammation. Pre-existing inflammation can mean pre-existing asthma particularly in condition of smoking during pregnancy and fetal passive smoking.^{7,8,12} Viruses like inflammation thus there does zero-polymorphism of IL-8, IL-10 and toll-like receptors what contribute developing of responsiveness to allergens, harmful factors and microbes (Clostridia, Staphylococcus) in fetus. This is reason for high and fast colonization of neonatal intestinal tract by Clostridia and Staphylococcus and very weak and

slow colonization of Lactobacillus and Bifidobacterium as in infant feeding on cow's milk or other artificial nutrition. If in mouth there is a toleration to Enterococcus and Streptococcus we can find pre-bronchiolitis inflammation and bronchoopstruction in that child. After birth in infant there are down regulation of mast cells and eosinophils.^{13,14,15} Immunoglobulin G(IgG) in atopic child is blocking antibody in inflamed mucosa and doesn't bind to mast cells. Immunoglobulin A(IgA) covers mucosal surface and inhibit attachment of microbes¹⁰ and high it level reduces the risk of IgE allergic disease. Against this, non-atopic infant has very early colonization with Bifidobacterium as breast feeding infants.

The purpose of this study was to investigate the effectiveness and the optimal time of supplementation with synbiotic in atopic children with common respiratory and/or ear infections. The children are fed daily at a dose preparation of synbiotic (Lactobacillus helveticus Rosell-52, Bifidobacterium infantis Rosell-33, Bifidobacterium bifidus Rosell-71 and fructo-oligosaccharides 750mg).

PATIENTS AND METHODS

We recruited inpatients children that couldn't be treat of respiratory infection in primary care health but hospitalized. During hospitalization they are selected using method unintentional sample, by respiratory infection and/or ear infection, by atopic status and by low level of immunoglobulins(Ig), particular IgA. In the same time their infections have been adequate treated and we established their immunologic state. After hospitalization treatment was followed by synbiotic during 3 or 6 months and we observed clinical features and level of immunoglobulins, particular IgA. Synbiotic was prescribe once a day, every 3 months IgA level was determined and in accordance with the outcome decided the termination or continuation of supplementation with synbiotics.

Atopic status are estimated by allergy skin prick test and graduated as high, low and no-atopics. The children who show sensitization with induration greater than 8 mm in total or each allergens (dermatophagoides pteronyssinus, mold, cockroach, cat, hair, latex, hornet, plumage, house dust, tree pollens, weeds pollens, grass pollens, dog hair, yellow egg, milk, seafood, peanut, cacao, kiwi, pork meat, rice, lemon, spinach, white egg, chicken meat, wheat flour) have the high atopic status. The children who show sensitization with induration less than 7 mm in total or each allergens have low atopic status. Children are non-atopics if have not sensitization to each of 25 allergens.

Range of normal values of immunoglobulins in serum are: for IgA 0,7-4 g/l, for IgG 7-16 g/l and for IgM 0,4-2,3 g/l, measured by Makler® ILAB.

We estimated that a sample size of 31 patients would be needed to obtain data at the 5% significance level with 90% power, assuming on 2SD. Time was included as a categorical parameter and using analysis of covariance. Covariates used for analyses, where applicable, were age, sex, atopic status and kind of illness. It was calculated confidence limits.

RESULTS

We recruited 31 inpatients children aged 6 to 42 months hospitalized because respiratory infections. Their average age was 19 months ($X_{av}=19\pm 19$, $p<0,05$). They were group of children with equal distribution by gender, 16 (52%) boys and 15 (48%) girls (figures 1 and 2).

Figure 1. Distribution by gender in children who suffer from respiratory infections (n=31)

Figure 2. Ages of children suffer from respiratory infection (in months)

During hospitalization we established that 14 children (45%) suffer from pneumonia, 8 (26%) suffer from middle ear infection and 23 (74%) suffer from pharyngitis. We found concomitant infections in 5 (16%) of patients (laryngitis in 1 (3%), sepsis in 2 (6%), urinary tract infection in 2 (6%) patients) and concomitant diseases (anemia in 8 (26%), enlarge

adenoids in 2 (6%), eczema in 4 (13%), wheezing bronchitis in 5 (16%), bronchial asthma in 13 (42%), urticaria in 1 (3%) patients). Data are shown at figure 3. By allergy skin prick test we estimated that 16 (52%) children are high atopics and 9 (32%) children are low atopics what is total 25 children (81%). Non-atopic are 6 (19%) children (figure 3).

Figure 3. Illnesses and atopic state in children suffer from immunodeficiency before treated by synbiotic

Before treatment with synbiotic, levels of immunoglobulin A are low in all patients, in average level of $0,33\pm 3,42$ g/l ($p<0,05$) what is lower than range of normal values of 0,7-4 g/l and levels of immunoglobulin G are low in 18 (58%) patients, in average level of $6,72\pm 5,04$ g/l ($p<0,05$) what is some lower than normal range values of 7-16 g/l and levels of immunoglobulin M are majority normal, except in 2 patients (6%), in average level of $0,97\pm 0,72$ g/l ($p<0,05$) (figure 4).

Figure 4. Values of immunoglobulins in atopic children with respiratory infection (g/l)

After 3 months treatment with synbiotic level of IgA increased for 1,8 times up to $0,6\pm 0,78$ g/l in 11 children (35%) and after 6 months treatment by synbiotic level of IgA increased for 3,9 times up to $1,3\pm 1,76$ g/l in 25 children (81%) (figure 5). Difference between 3 and 6 months

treatment by synbiotic isn't significant ($t=0,43$, $P<0,05$) but after 3 months treatment with synbiotic as after 6 months treatment no one child suffers from respiratory infections what is important clinical finding.

DISCUSSION

A meta-analysis collecting studies published during last decade (13) show that the potential field of application of probiotics is wide but still not thoroughly clarified, it was confirmed a real beneficial and immune-modulating effect of probiotics in some allergic and respiratory illnesses according to specific strain and the appropriate time. Our intention was to clarify optimal duration of treatment with synbiotic and our finding is at least 6 months.

Consistent changes were seen in the treatment kind of illness and level of immunoglobulins suggesting deficiency of humoral immunity. At fact, we found low level of protective immunoglobulin A in all young children average age of 19 months and every second child (58%) showed deficiency of IgG. Level of IgM is normal in 94% studied children that suffer from respiratory infections. Every second child average age of 19 months suffers, at the same time, from pneumonia (45%) and deficiency of humoral immunity. Every fourth child suffers, at the same time, from middle ear infection (26%) and deficiency of humoral immunity. In every fourth child we established, at the same time, anemia (26%) and deficiency of humoral immunity. Wheezing disorders (as wheezing bronchitis and bronchial asthma), are established in every second child ($n=18$ or 58%) old 19 months, who, at the same time, suffer from deficiency of humoral immunity and respiratory infections needed to treat in hospital.

Concomitant infections (laryngitis, sepsis, urinary tract infection) was found in every 6 child (16%), average old 19 months, with deficiency of immunoglobulin A and G. It is well known that children reach normal values of immunoglobulins by the end first year of life.

After 3 months of treatment with synbiotic every third child (35%) acquired normal level of IgA and after 6 months of same treatment 81% children acquired normal level of IgA. This dates means that synbiotic is very effective in solving of deficiency of IgA and IgG and following respiratory infections but duration of supplementation of synbiotic must be the shortest 6 months. Important clinical improvement was found after 3 months of supplementation with synbiotics so that no child is sick from an infection (respiratory, sepsis, inflammation of the middle ear).

Influence of many environmental and microbes agents during the first 3-4 years of life are known to affect immune system particular respiratory immunity, lung and airways development, possible evolution of asthma and allergy, probable pharyngitis, possible pneumonia, middle ear infection and anemia. These early influences on the respiratory system in young children result to burden of respiratory and hematologic diseases followed by deficiency of humoral immunity. With atopic children immunity answer to infective agents is in keeping with down-regulation of eosinophil and mast cells. We showed that synbiotic respectively probiotic takes right place for the successful control of respiratory infections in atopic young children.

In atopic children immunity answer to infective agents is in keeping with down-regulation of eosinophil and mast cells. Disbalance of intestinal microbiota and local intestinal deficit of IgA influence to low level of respiratory IgA in atopic children what is reason for frequent respiratory and other, possible severe infections, and anemia, then their long-time of duration. Our intention was to clarify optimal duration of treatment with synbiotic and we confirm that it is at least 6 months. We emphasize that we have already achieved clinical improvement after 3 months of supplementation with synbiotic. Synbiotic reduce the risk of common infectious disease in young, atopic, children.

REFERENCES

1. Guidelines for the Evaluation of Probiotics in Food. Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food. London Ontario, Canada, April 30 and May 1, 2002 (http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf)
2. Delcenserie V, Martel D, Lamoureux M, Amiot J, Boutin Y, Roy D. Immunomodulatory effects of probiotics in the intestinal tract. *Curr Issues Mol Biol* 2008; 10: 37-54.
3. Kent LE, Hubbard NE. Probiotic immunomodulation in health and disease. *J Nutr* 2000; 130: 403S-409S.
4. Maldonado Galdeano C, Perdigon G. proposed model: mechanisms of immunomodulation induced by probiotic bacteria. *Clin Vaccine Immunol* 2007; 14: 485-92.
5. Przemyslaw JT, Piotr T. Probiotics and prebiotics. *Cereal Chem* 2003; 80: 113-7.
6. Reid G, Sanders ME, Gaskins HR, et al. New scientific paradigms for probiotics and prebiotics. *J Clin Gastroenterol* 2003; 37: 105-8.
7. Famularo G, Moretti S, Marcellini S, DeSimone C. Stimulation of immunity by probiotics. In: Fuller R, ed. *Probiotics 2: applications and practical aspects* London: Chapman & Hall, 1997: 133-61.
8. Boirivant M, Strober W. The mechanism of action of probiotics. *Curr Opin Gastroenterol* 2007; 23: 679-92.
9. Ozdemir O. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. *Clin Exp Immunol* 2010; 160: 295-304.
10. Kukkonen K, Kuitunen M, Haahtela T, Korpela R, Poussa T, Savilahti E. High intestinal IgA associates with reduced risk of IgE-associated allergic diseases. *Pediatr Allergy Immunol* 2010; 21: 67-73.
11. ProbiokidR ImmunoR. Product Information. Belgrade: "Ivančić i sinovi", 2009. (in Serbian).
12. Weichert S, Schroten H, Adam R. The role of prebiotics and probiotics in prevention and treatment of childhood infectious diseases. *Pediatr Infect Dis J* 2012; 31: 859-62.
13. Latzin P, Roosli M, Huss A, Kuehni CE, Frey U. Air pollution during pregnancy and lung function in newborns: a birth cohort study. *Eur Respir J* 2009; 33: 594-603.
14. del Giudice MM, Leonardi S, Ciprandi G, et al. Probiotics in childhood. Allergic illness and respiratory infections. *J Clin Gastroenterol* 2012; 46: 69-72.
15. Cocurullo G, Campana G, Valenti N, et al. Probiotics and asthma, new insight. *The Child* 2012; 1: 2-3.