Romanian Biotechnological Letters *Vol. 22, No. 2, 2017*
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ORIGINAL PAPER

Probiotics as a therapeutic option to reduce the duration of upper respiratory tract infections in children

Received for publication, January 10, 2015
Accepted, September 08, 2016

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Abstract

Acute respiratory tract infections are the most common reason for attending primary care appointments and accounts for 80% of antibiotic prescriptions. This minireview is aiming to highlight on the use of probiotics in the therapeutic management of upper respiratory tract infections (URTI). The URTIs can alter the body's immune system leaving it at risk for other infections. Many studies also showed that gastrointestinal (GI) microbiota plays a key role in immune adaptation, any intestinal dysbiosis predisposing the patients to more frequent and more aggressive respiratory tract infections. A common problem in treating the URTIs is the overuse of antibiotics. Moreover, inappropriate and wide use of antibiotics may lead to the development of bacterial resistance and disturb the normal balance of human microbiota, facilitating the pathogen colonization and reducing availability of vaccines used for viral infections treatment. We present tan overview of studies performed mainly in children which have shown that orally administered probiotics may prevent, reduce the duration and the intensity of the clinical symptoms inURTIs. However, although some studies showed that probiotics can be effective in increasing the quality of life and decreasing the morbidity and mortality around the URTIs there is yet not enough proof to postulate that probiotics can be used alone in the treatment or prevention of these infections, and no certified treatment protocol using probiotics (alone or in association with other drugs used for URTIs) is available.

Keywords: probiotics, upper respiratory tract infection, antibiotics, viral infections

1. Introduction

A large number of authors conducted in the last years several studies to evaluate the role of the probiotics in preventing acute upper respiratory tract infections or in shortening their illness duration [1, 2]. Most children younger than 2 years, experience several RTIs (respiratory tract infections) during the first year of life, and one-quarter suffer from recurrent or prolonged infections even in developed countries. [3]. RTIs refer to a number of infectious diseases involving the respiratory tract, and are normally further classified as an URTI (upper respiratory tract infections) or a LRTI (lower respiratory tract infections). Typically, URTIs include tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, certain types of influenza, and the common cold. Symptoms of URTIs can include cough, sore throat, running nose, nasal congestion, headache, low-grade fever, facial pressure or pain, and sneezing. The most common LRTIs are bronchitis and pneumonia, and are generally more serious than URTIs [4]. The

most common pathologies involved in the studies were acute sinusitis, tonsillitis and common cold. Usually, the studies would be conducted on adults but we also found several trials which studied the response of medical treatment on children patients [5]. RTIs remain a major challenge for global public health by causing morbidity and mortality among children. Global Burden of Disease Pediatrics Collaboration reported that LRTIs were the leading causes of death among younger children aged up to five years old in 2013 [6].

Probiotics are live bacteria and yeasts that are good for our health, and are believed to provide us health benefits when we ingest them. We usually think of bacteria as something that causes diseases. But our body is full of bacteria, both good and bad. Probiotics are often called "good" or "helpful" bacteria because they help keep your gut healthy [7]. They are defined by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) as "live microorganisms that, when administered in adequate amounts as part of food, confer beneficial effects to the host through his intestinal microbiota". You can also find them in some foods and supplements [8]. It's only been since about the mid 1990s that people wanted to know more about probiotics and their health benefits. Some of the probiotics strains are commensal microorganism, naturally found in our body. The most commonly strains used in commercial products, alone or in associations, are: *Lactobacillus, Streptococcus* and *Bifidobacterium*. They can be administrated in all kinds of food in their powder form, or they can be ingested with water and there is no need for a prescription while using them.Upper respiratory tract infections are a type of diseases that are very common in children, representing an important part of the pediatric morbidity worldwide. Usually, when children get sick, parents have to stay at home and so this infection have a high economic impact on the society and because they are highly contagious they represent an important challenge for public health.Viral infections are the main cause of respiratory tract infections so the first line of treatment usually does not begin with antibiotics. For some of the viruses, there have been developed vaccines but there are still a large number of viruses that are not influenced by the vaccines so in viral respiratory infections the adequate treatment must be initiated immediately in order to avoid bacterial infection. The overuse of antibiotics used by pediatricians, ENT specialists and general practitioners in the last decade, increases the risk for bacterial resistance and disturb the normal microbiota, facilitating the pathogen colonization [9, 10]. Probiotics may exert a wide range of beneficial effects, such as balancing the host gut microbiota and interacting with the innate and adaptive immune system, which may promote resistance against pathogens [11, 8].

A lot of clinical studies focusing on evaluating the health benefits of probiotic foods containing well-defined probiotic strains have been conducted in many countries. For example, *S boulardii, Lactobacillus rhamnosus* GG, and *Lactobacillus reuteri* DSM 17938 were used to treat acute gastroenteritis IBS [12], and antibiotic-associated diarrhea in children and adult patients. *Bifidobacterium animalis* subsp. lactis strain BB-12 was used to prevent nosocomial infections, and *Bifidobacterium lactis* DN-173 010 was used to treat functional constipation in children [13]. The effects of probiotic products may depend on the amount ingested and the pattern of consumption.

2. Materials and Methods

We accessed four electronic databases [MEDLINE/PubMed, Scopus (Elsevier), Web of Science, and Cochrane (Cochrane VHL)], as well as ClinicalTrials.gov until January 2015, using methodological approaches described in the Cochrane Handbook for Systematic Reviews [14].We took in consideration as eligible studies randomized clinical trials of any

duration (phase III studies) that compared strains of probiotics in any form of administration to placebo in apparently healthy children (0 to 18 years of age) who at some point developed an upper respiratory tract infection.We didn't take into account a certain dose of probiotic, only it's administration or if it was combined with any other drug (vitamins, antibiotics, anti-inflammatory). We only used English, French and Romanian languages result because of the language limitation and we were interested in the duration of the symptoms, the quality of life during the episodes, the recurrences and the side effects or unexpected events.We excluded the following: animal studies, studies on children with chronic or congenital diseases, studies on another organs and studies in other languages.The duration of probiotic treatment ranged from 5 days to 12 months, and most trials were carried out for more than three months during the winter season.We were able to use 10 studies that analyzed 2376 kids. The participants were randomized to take probiotics or placebo but the doze and the compliance of the patient were not very specific.Most studies provided 109 or 1010 colony-forming units (CFUs) of probiotics per day for 3 to 8 months. Studies have shown that an important percent of children develop upper respiratory tract infections that usually lasted for 7 days and also 23% of them were treated with antibiotics.

3. Results and discussion

In order to analyses the efficacy of probiotics in the upper respiratory tract infection treatment, the main objectives of studies were to evaluate the effect of probiotics on the number of subjects with at least one RTI episode, the effect of probiotic on the duration of RTI episodes and thus, on the days absent from day care/school, the number of side-effects. Because the main social problem is the number of days-off that the parent has to take, we also added these information, in order to summarize the loss of work force and money for the time spent at home with the sick child.

Efficiency of probiotics on the number of subjects with at least one RTI episode

Hojsak et al. showed that 60 children out of 139 that were administrated probiotics, had events during that period of time. In the group that was treated with placebo, 43,16% from those treated with probiotics and 69% from the group without probiotics developed respiratory infections during the winter months [15]. There is also another study stating that 64 out of 113 children (57.14%) who received probiotics vs 72 out of 113 (63.7%) with placebo, developed respiratory infections during the same period [16]. Both results show that children who received probiotics during the winter months had better chances not to develop respiratory infections.

Efficiency of probiotic on the illness duration of RTI episodes

The studies that were analyzed showed a mean of 5 days for complete recovery in the group that was treated with probiotics vs 7 days forcomplete recovery in the group that was administrated regular treatment. That means 30% less illness days for each episode. This effect is probably due to the probiotic's capacity of interacting with the innate and adaptive immune system, which may promote resistance against pathogens.

Efficiency of probiotics on the days absent from day care/school

Gerasimov et al. stated 7 days absent from school in the group that was administrated probiotics and 9 days absent from school in the placebo group. Hosjak stated 3.1 vs 5.1 days absent from school. Therefore, the mean of days absent from school were 4.9 for the group with probiotics administration vs 5.8 for the placebo group.

Efficiency of probiotics on the number of adverse events

The trials we've reviewed did not identify any side-effects related to treatment protocol including probiotic and placebo during the study period. One study noted a severe

intensity of abdominal pain in the placebo group and an otitis media in the symbiotic group [17].

Efficiency of probiotics on the anti-infectious immunity

Potential underlying mechanisms of the action of probiotics on RTIs are not well defined yet. In addition to the local effects of competitively colonizing the gut to exclude potential pathogens, modulating the gut barrier function, and permeability, probiotics have been shown to have various immunomodulatory effects in the host [18]. It has been shown that probiotics can influence both innate and adaptive immune responses by producing exopolysaccharides. A study showed that probiotics could increase the leukocyte, neutrophil granulocytes, and natural killer cell counts and activity [19]. They also were able to increase the expression of interleukin (IL)-10 and decrease the inflammatory cytokine expression, such as tumor necrosis factor-α, IL-1β, and IL-8. Furthermore, probiotics can maintain higher salivary immunoglobulin A levels and some of them (*Lactobacillus reuteri*) can reduce the incidence of common antibiotic related side-effects, inhibit disease-causing bacteria in the gastro-intestinal tract and enhance the immune system by increasing the number of immune cells in the body [20].

Limitations of the review study

First, the probiotic strain, the duration of regimens, the administration forms, adult/child doses, and follow-up time differed across the included studies. Second, young children aged less than five years, especially less than two years, are more likely to get RTIs; the trials with the study population age ranging from newborn to 18 years old were included in the systematic review. Most of the trials did not report the outcomes of different age groups; it may cause some statistical bias of the over effect of probiotics on the incidence of RTIs. Third, we included only trials published in English; other languages, abstracts presented in conferences, and ongoing registered trials were not included.

4. Conclusion

Pooled data analysis showed that probiotic supplementation significantly decreased the number of subjects with at least one RTI episode. Evidence shows that children supplemented with probiotics had fewer numbers of days of RTIs per person, and had fewer numbers of days absent from day care/school compared with children who had taken a placebo.Although some of the results showed that probiotics can be effective in increasing the quality of life and decreasing the morbidity and mortality around the upper respiratory tract infections there is yet not enough proof to postulate that probiotics can be used alone in the treatment or prevention of the upper respiratory tract infection. For the moment, studies we reviewed do not provide on scientific basis a certified treatment protocol using probiotics (alone or in association with other drugs used for RTIs). However, the results are still very promising as the pathology is one of great interest and any kind of new discovery that can increase the quality of life would be a great step forward.

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