VERSITA

Cent. Eur. J. Med. • 7(3) • 2012 • 362-365
DOI: 10.2478/s11536-011-0160-8

Central European Journal of **Medicine**

Probiotic E.faecalis – adjuvant therapy in children with recurrent rhinosinusitis

Rapid Communication

Richard Kitz[1]*, Ute Martens[2]*, Egmont Zieseniß[3], Paul Enck[2], Markus A. Rose[1]

1 Children's Hospital, Goethe University, Theodor Stern Kai 7, D-60590 Frankfurt, Germany

2 Medical Hospital, Eberhard Karls University, Hoppe-Seyler-Straße 1, 72076 Tuebingen, Germany

3 inpharm consulting, Heidsieker Heide 114, 33739 Bielefeld, Germany

Received 4 July 2011; Accepted 16 February 2012

Abstract: Sinusitis is a frequent complication of respiratory tract infections. Probiotics are perceived to be useful in infections, allergies, and inflammations. Our prospective trial stratified 204 children with recurrent rhinosinusitis by age (2–11 years, 54m:64f; 12–18 years, 39m:47f) and assigned them to standard treatment (antibiotics, anticongestants) or additional 60 days Symbioflor-1 (SF1; Enterococcus faecalis 1.5-4.5x10^7 CFU). The number of sinusitis episodes was lower in SF1-treated patients (2.52±0.91) than among controls (3.27±1.36; p=0.01). Mean duration of the first sinusitis episode was 11.9±8.6 days with SF1, whereas it was 16.1±12.9 days in the younger controls (p=0.023) and 9.86±5.05 days in the elder controls (n.s.). Duration of subsequent sinusitis episodes was also shorter in SF1 patients (15.2±13.6 days) compared with controls (22.7±14.8 days; p=0.030). No adverse events were observed. Probiotic Enterococcus faecalis adjuvant to conventional therapy can reduce the number and duration of rhinosinusitis episodes in children and adolescents.

Keywords: *Probiotics • Recurrent rhinosinusitis • Adjuvant therapy • Children*

1. Background

Recurrent rhinosinusitis (RRS) is a frequent complication of upper respiratory tract infections in adults and also in children. Dysfunctions of ventilation and drainage of the nasal sinuses are assumed to be pathogenic causes. Whereas RRS in adults is characterized more by eosinophil-mediated mechanisms, lymphocytic inflammation predominates in children. A weakness of the innate local and peripheral immune defence is proposed as an underlying mechanism. A viral rhinosinusitis often precedes bacterial infection of the nasal sinuses. In RRS, *Staphylococcus aureus*, coagulase-negative staphylococci, *Pseudomonas aeruginosa*, and anaerobic bacteria can be isolated as solitary or mixed infections. Although symptoms lack specificity, clinical presentation encompasses nasal congestion, (purulent) rhinorrhoea, postnasal drip, headache, fever, upper jaw pain, vomiting, and general fatigue. Besides symptomatic treatment (pain relievers, anticongestants), causal therapy includes antibiotics, antihistamines, topical and/or systemic steroids, and surgical intervention. In adults with recurrent rhinosinusitis, probiotic *Enterococcus faecalis* has been shown to be effective via immune-stimulating mechanisms [1]. Probiotic food supplementation promotes the secretion of anti-infectious mediators and systemically supports anti-inflammatory processes. Our study is the first to investigate the impact, safety, and tolerability of probiotic *Enterococcus faecalis* when given in children as adjuvant therapy for RRS.

* *E-mail: Markus.Rose@kgu.de*

Table 1. Characteristics of the study population (mean ± SD)

	Age Group		SF1 (n=121)	Controls (n=83)	p
gender (m:f)	2 to 11		33 : 39	21 : 25	0.985
	12 to 18		24 : 25	15 : 22	0.4365
age (yrs)	2 to 11		5.87 ± 2.87	6.37 ± 2.65	0.345
	12 to 18		13.9 ± 1.89	14.7 ± 1.76	0.402
weight (kg)	2 to 11		23.1 ± 9.19	24.7 ± 8.90	0.350
	12 to 18		52.9 ± 12.7	55.6 ± 13.6	0.342
height (cm)	2 to 11		115.3 ± 21.3	117.2 ± 18.0	0.627
	12 to 18		159.1 ± 10.0	161.1 ± 11.05	0.377
		severity			
sinusitis episode at study entrance	2 to 11	mild	12 (16.7)	15 (32.6)	0.078
		moderate	40 (55.6)	24 (52.2)	
		severe	20 (27.8)	7 (15.2)	
	12 to 18	mild	6 (12.2)	6 (16.2)	0.716
		moderate	32 (65.3)	21 (56.8)	
		severe	11 (22.4)	10 (27.0)	

2. Methods

In this prospective phase IV trial, 204 children with RRS (at least 4–6 episodes/year) were assigned by the treating physician arbitrarily to standard sinusitis treatment (amoxicillin 7 days, nasal anticongestants TID) followed by 8 weeks of probiotic *Enterococcus faecalis* (cells and autolysate of 1.5 to 4.5 x 10^7 CFU; 3 x 20 droplets/d) in suspension (Symbioflor-1®, SF-1; SymbioPharm, Herborn, Germany), or no probiotic treatment. Inclusion criteria were age 2–18 years and a doctor's diagnosed recurrent rhinosinusitis. Exclusion criteria were immunodeficiency, gastroesophageal reflux, cystic fibrosis, bronchial asthma, pertussis, allergic rhinoconjunctivitis, and previous treatment with SF1. The study population was recruited by 15 pediatric practitioners during the winter season 2007/2008 and stratified into two age groups (2–11 and 12–18 years).

To assess the intervention, the duration and recurrence of sinusitis episodes were documented for 6 months beginning with the first episode. Primary endpoints were the mean duration and frequency of sinusitis episodes per patient. Data from both groups were compared using Student's t- and Chi-square tests, and a probability (p) level of 95% ($p<0.05$) was considered significant. All guardians supplied written informed consent prior to the study. Human experimentation guidelines of the German Drug Act and the Declaration of Helsinki / Hong Kong were followed.

3. Results

Of 204 children (111 girls and 93 boys), 121 (59.3%) received combined standard therapy and SF1, while 83 (40.7%) received only the standard treatment (Table 1). The distribution by treatment mode was similar in both age groups: 61.0% versus 39% in children age 2 to 11, and 57.0% versus 43% in those aged 12 to 18. No significant differences were noted for the severity of the sinusitis prior to treatment; however, in the younger age group, physicians tended to assign more patients with severe rhinosinusitis to additionally SF1 ($\chi 2=5.112$, $p=0.078$).

The number of sinusitis episodes was significantly lower in SF1 treated patients as compared with controls (Table 2). We also observed a positive impact for SF1 on the duration of the rhinosinusitis episodes. The severity of sinusitis was similar in patients treated with and in those without SF1.

Doctors assessed the safety and tolerability of SF1 as "good" or "very good" in the majority of cases, and comparison between both management arms showed

Table 2. Number and duration of sinusitis episodes with therapy (mean ± SD)

	Age Group	SF1 (n=121)	Controls (n=83)	p
number of episodes	2 to 11	2.46 ± 0.90	3.04 ± 1.09	0.049
	12 to 18	2.61 ± 0.93	3.54 ± 1.16	0.042
duration of first episode	2 to 11	11.4 ± 5.05	16.1 ± 12.9	0.023
	12 to 18	12.5 ± 10.3	9.86 ± 5.05	0.123
duration of other episodes	2 to 11	14.6 ± 14.2	24.9 ± 16.1	0.020
	12 to 18	16.2 ± 12.70	19.9 ± 12.7	0.030

superiority of additional SF1 compared with controls. No adverse events were noted, and general assessment of tolerability (rated of a 5-point VAS scale between "very good" and "insufficient") by doctors and by parents approved the general acceptance of SF1 therapy; no difference was noted between SF1 and controls for either age group.

4. Discussion

Recurrent rhinosinusitis (RRS) is a challenging entity with a complex pathophysiology, consisting of underlying conditions (e.g., anatomical obstruction, defects in the mucociliary clearance system, immunodeficiency, allergy, gastroesophageal reflux disease), infections, and environmental factors. Although the mainstay of treatment is antibiotic therapy, a large number of patients prove to be refractory even to long courses of broad-spectrum agents. This has led to the exploration of alternative treatments. Previous studies have demonstrated the efficacy of probiotics for the prevention of allergic sensitization [2], in treatment of allergic rhinitis [3], and respiratory tract infections [4]. These protective effects might be explained by the observation that probiotic bacteria produce inhibitory substances against common pathogens, thus supporting the host in the fight against infections [5]. Our results show an overall positive impact of SF1 in paediatric RRS. The observed effects were the strongest in the younger age group, making this easy-to-administer, painless, and safe adjuvant therapy even more attractive for children and their parents.

While some interventional studies have shown that probiotics may be used in addition to conventional management strategies to prevent or treat rhinosinusitis, others have produced conflicting results. In another recent trial, 3 months of probiotic *Lactobacillus casei* significantly decreased the number and duration of rhinopharyngitis [6]. In adults suffering from RRS, 4 weeks of probiotic *Lactobacillus rhamnosus* significantly improved the clinical symptom score, but after 8 weeks no differences could be found compared to placebo [7].

Part of these differences may result from different bacterial strains that have been used in these studies and that may exert different immunological effects, as demonstrated in a placebo-controlled trial where a comparison of various probiotics revealed a heterogeneous impact on febrile airway infections in children [4]. The duration of the probiotic treatment may also be of importance. A clinical trial on probiotics in preschool children showed that fewer rhinitis episodes occurred in the latter half of the study, indicating that probiotic-induced modulation might depend on longer treatment periods [8]. The majority of the studies with probiotics for rhinological symptom improvement have been done in patients with seasonal or perennial allergic rhinitis. It is possible that patients with RRS may have other factors, such as intermittent use of antibiotics and steroids for acute flare-ups, that may interfere with an optimum immunomodulatory probiotic response.

In RRS, antibiotic therapy can fail because of biofilm growth, as documented in surgical specimens obtained from inflamed sinuses in patients with chronic rhinosinusitis. A bacterial biofilm consists of a colony of microbial cells that live within a self-produced polysaccharide matrix, and are strongly adherent to a living or inert surface. In a recent *in vitro* study, commonly used probiotic bacteria significantly decreased biofilm formation and viability of *Streptococcus mutans* [9], thus explaining another possible mechanism of action of probiotic bacteria in RRS. Germs unresponsive to common antibiotics can also complicate RRS. Of particular interest, in intensive care unit patients, probiotic food supplementation significantly inhibited *Pseudomonas aeruginosa* growth [10].

The goal of this pilot study was to evaluate probiotic *Enterococcus faecalis* in a real life setting, and the positive results will stimulate future research. Strengths of our study include the prospective controlled design and the patient-oriented outcomes. Our observational trial had inherent limitations, including the presence of multiple confounding variables and possible observer bias. As with all studies in young children, we relied on care givers' accurate reporting of the children's symptoms and accepted the limitations of this approach. With regard to the young age of many of our study participants, we could not use established and validated rhinosinusitis scoring instruments (e.g., the Sinonasal Outcome Test SNOT-20). Assignment to either SF1 or control group was not randomized but left to the decision of the treating physician. Despite both groups being balanced in their demographics and their basic clinical characteristics, it cannot be excluded that the paediatricians have used selection criteria that remain undisclosed and may have biased the results. One such bias may be that children with more severe sinusitis were more likely to receive SF1 in addition to conventional therapy. But even if sicker patients were preferentially treated with SF-1, our data even emphasize its efficiency. Finally, stricter definition of sinusitis pathomechanisms, e.g., supported by laboratory testing for viral or bacterial origin, may be superior to clinical definitions and may have corroborated the results. However, the advantages of an observational study under clinical routine conditions have to be weighted against these restrictions. Prospective randomized controlled studies should be designed to validate these findings.

Acknowledgement /Conflict of Interest

The first authors (RK & UM) have advised the study, written the manuscript, and declare no conflict of interests. EZ has evaluated the observational study based on a consulting contract with the sponsoring company (SymbioPharm, Herborn, Germany). PE performed the statistics and has a consulting contract with the sponsoring company. MR supported the study design, revised the manuscript, and has received financial support from SymbioPharm for scientific projects.

References

[1] W. Habermann, K. Zimmermann, H. Skarabis, R. Kunze, and V. Rusch. Reduction of acute recurrence in patients with chronic recurrent hypertrophic sinusitis by treatment with a bacterial immunostimulant (Enterococcus faecalis bacteriae of human origin). Drug Research, 2002, 52, 622-627

[2] M.A. Rose, F. Stieglitz, A. Köksal, R. Schubert, J. Schulze, and S. Zielen. Efficacy of probiotic Lactobacillus GG on allergic sensitization and asthma in infants at risk. Clin. Exp. Allergy, 2010, 30(9),1398-4058

[3] Y . Ishida, F. Nakamura, H. Kanzato, D. Sawada, H. Hirata, A. Nishimura et al. Clinical effects of Lactobacillus acidophilus strain L-92 on perennial allergic rhinitis: a double-blind, placebo controlled study. J. Dairy Sci., 2005, 88(2), 527-533

[4] Z. Weizman, G. Asli, A. Alsheikh. Effect of a Probiotic Infant Formula on Infections in Child Care Centers: Comparison of Two Probiotic Agents. Pediatrics 2005, 115, 5-9

[5] M. Silva, N.V. Jacobus, C. Deneke, and S.L. Gorbach. Antimicrobial substance from a human lactobacillus strain. Antimicrob. Agents Chemother. 1987, 31(8), 1231-1233

[6] E. Guillemard, F. Tondu, F. Lacoin, and J. Schrezenmeir. Consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114001 reduces the duration of respiratory infections in the elderly in a randomised controlled trial. Br. J. Nutr. 2010, 103, 58-68

[7] S.S. Mukerji, M.A. Pynnonen, H.M. Kim, A. Singer, M. Tabor, J.E. Terrell. Probiotics as adjunctive treatment for chronic rhinosinusitis: a randomized controlled trial. Otolaryngol. Head Neck Surg. 2009, 140, 202-208

[8] M. Giovannini, C. Agostoni, E. Riva, F. Salvini, A. Ruscitto, G.V. Zuccotti et al. A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing Lactobacillus casei in pre-school children with allergic asthma and/or rhinitis. Pediatr. Res., 2007, 62(2), 215-220

[9] E.M. Söderling, A.M. Marttinen, and A.L. Haukioja. Probiotic Lactobacilli interfere with Streptococcus mutans biofilm formation in vitro. Curr. Microbiol. 2011, 62(2), 618-622

[10] C. Forestier, D. Guelon, V. Cluytens, T. Gillart, J. Sirot, and C. de Champs. Oral probiotic and prevention of P. aeruginosa infections: a randomized, double-blind, placebo-controlled pilot study in intensive care unit patients. Critical Care, 2008, 12(3),R69