ORIGINAL RESEARCH PAPER

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CLINICAL EVALUATION OF THE THERAPEUTIC USE OF ORAL PROBIOTIC STREPTOCOCCUS SALIVARIUS K12 FOR RECURRENT PHARYNGITIS AND/OR TONSILLITIS

KEY WORDS: Streptococcus salivarius K12, Bactoblis®, pharyngitis, tonsillitis

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ABSTRACT

The most important and common bacterial cause of pharyngeal infections in humans is Streptococcus pyogenes. The oral probiotic Streptococcus salivarius K12 has been studied and shown that it clearly antagonizes the growth of Streptococcus pyogenes by releasing two bacteriocins, salivaricin A2 and salivaricin B. This oral probiotic is quite safe and because of its ability to colonize the oral cavity, we have studied its efficacy in reducing the incidence of streptococcal pharyngitis and/or tonsillitis.The study included 34 patients with recurrent streptococcal pharyngitis or tonsillitis, aged between 12 years old and 45 years old. 20 patients were treated daily for 90 days with an oral slow-release tablet containing five billion colony-forming units of S. salivarius K12 (Bactoblis®), and 14 patients selected as untreated control group. 10 healthy patients were used as an additional control group. After 3 months of treatment, a 3-month follow-up period without treatment was included to evaluate a possible persistent protective role for the previously administered product. The patients who completed the 3-month course of Bactoblis showed a dramatic decrease in their episodes of streptococcal pharyngeal infection (about 95%) comparing infection episodes with the previous year. Patients tolerated the product well, with no side effects reported. Prophylactic administration of S. salivarius K12 to patients with a history of recurrent oral streptococcal pathology decreased the episodes of streptococcal pharyngeal infections and/or tonsillitis.

Introduction:

Probiotics use has been widely studied for gastrointestinal health (1). Since the oral cavity is not a separate part of the body, and also both periodontal diseases, some pharyngeal and tonsiller diseases and dental caries have bacterial causes, a probiotics use to treat these maladies is currently being evaluated (1-3). Several over-the-counter products have been formulated with probiotics and suitable for oral care (1-3). Streptococcus salivarius K12, BLIS (bacteriocin-like inhibitory substance) K12, was isolated in New Zealand from the mouth of a child (4). It releases two high efficient bacteriocins named salivaricin A2 and salivaricin B (4). BLIS K12 can effectively inhibit the growth of β-hemolytic (group A) Streptococcus pyogenes, a common cause of pharyngitis, tonsillitis by secreting these bacteriosins (4).

BLIS K12 has been shown to inhibit the growth of Moraxella catarrhalis, Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus anginosus, Micrococcus luteus, Eubacterium saburreum, and Micromonas micros (5). BLIS K12 colonizes within oral cavity, nasopharyngeal and adenoid tissues and with good persistence, it can still be detected 32 days later (6). We have decided to evaluate the preventive role of BLIS K12 on the patients who have recurrent history of streptococcal pharyngitis and/or tonsillitis because of its good colonization capability and very high safety profile, combined with its ability to directly counteract oral pathology. Our main target was reducing the number of episodes of streptococcal pharyngitis and/or tonsillitis.

Materials and methods

This study was conducted during routine outpatient work following international guidelines and in line with the principles outlined in the Declaration of Helsinki, so approval from local ethics boards was not required. The study was carried out in Otolaryngology clinic of Ankara Medicalpark Hospital. The study included 34 patients with recurrent streptococcal pharyngitis or tonsillitis, aged between 12 years old and 45 years old. Inclusion criterias were: total absence of symptoms of infective disease at the time of enrollment; and diagnosis of recurrent streptococcal (group A hemolytic Streptococcus) pharyngitis and/or tonsillitis in the previous year. Exclusion criterias were diagnosis of obstructive sleep apnea syndrome, asthma, excessive systemic diseases. 34 patients who admitted to our clinic between October 2015 and January 2017 were included in this study. All of the patients have a history of more than three episodes of recurrent pharyngitis and/or tonsillitis in the previous year confirmed by throat swab (positive for group A hemolytic Streptococcus). 20 out of the 34 patients with recurrent disease were selected as the BLIS K12 group and 14 as the no-BLIS K12 group. 10 other patients were enrolled without a history of recurrent pathology were selected as a not-recurrent no-BLIS K12 group. The recurrent-BLIS K12 (n = 20), recurrent-no-BLIS K12 (n = 14), and not-recurrent-no-BLIS K12 (n = 10) subjects were followed for 90 days. Another 90 days follow-up were added for the recurrent-BLIS K12 and recurrent-no-BLIS K12 groups during which the product was not administered.

Bactoblis® contains five billion colony-forming units per tablet of S. salivarius K12 ATCC BAA-1 024 (BLIS Technologies Ltd, North Dunedin, New Zealand) and is manufactured by SIIT, (Trezzano S/N, Milan, Italy). The product is administered as one tablet daily for 90 days. The product, an oral, round-shaped, vanilla-tasting, slow-release tablet (dissolving in about 5 minutes) is administered just before bedtime (ie, after teeth brushing and/or mouthwashing). Correct administration of the product requires that the tablet is not chewed or directly swallowed, but is sucked for about 4–5 minutes. Before administration of the tablet, a chlorhexidine mouthwash is advised in order to enhance the colonization process of the strain, reducing extreme competition from endogenous S. salivarius inhabiting the mouth.

We evaluated the results by medical examinations, throat swabs, episodes of pharyngitis, tonsillitis, in the recurrent-BLIS K12, recurrent-no-BLIS K12, and not-recurrent-no-BLIS K12 groups during 90 days of treatment with the product and during the follow-up period. We also evaluated the side effects and tolerability of the product.

Statistical analysis

The statistical analysis was performed using the Vandenbroucke method which uses standardized incidence ratio and its confidence interval 100 (1 - α) % (7).12 If the range includes 100%, it is most likely that the difference between observed and expected values is due to chance (random fluctuations in the data). If the confidence interval does not include 100%, it is very likely that the difference is not due to chance. The statistical comparisons are shown in Table 2.

Results

In this study, our main aim was to determine the efficacy of BLIS K12 on patients with a history of recurrent pharyngitis and/or tonsillitis of streptococcal origin. The efficacy of BLIS K12 was determined by the number of episodes of oral streptococcal pathology before and after the therapy. The 34 patients were enrolled in this study and each was assigned to one of these two groups, recurrent-BLIS K12, recurrent-no-BLIS K12, and 10 other patients without a history of recurrent pathology were assigned in not-recurrent-no-BLIS K12 group. Demographic characteristics of

the patients were summarized in table 1.

Statistically significant results were observed during the 90 days of treatment with BLIS K12 (Table 2) in terms of episodes of streptococcal pharyngitis and/or tonsillitis in the 20 patients having had more than three episodes of streptococcal pharyngitis and/or tonsillitis in the previous year. These 20 patients had suffered 118 episodes in 12 months, and during the 90 days of treatment, only two episodes of streptococcal infection were diagnosed. The calculated incidence per month per patient dropped from 0.29 to 0.024.

The control group, (patients with a diagnosis of recurrent oral streptococcal disease without having the regiment of BLIS K12) showed no difference of number of episodes of streptococcal pharyngitis and/or tonsillitis when we compared it to the previous year.

The other controls, (not-recurrent no-BLIS K12 enrolled without a diagnosis of recurrent oral streptococcal disease) showed no difference of number of episodes of streptococcal pharyngitis and/or tonsillitis when we compared it to the previous year.

The evaluation of tolerability, compliance, and side effects is reported only for the recurrent-treated group as enrolled in terms of number (n = 20). No patients declared any side effects or intolerability to the product.

To determine the protective role of BLIS K1, we followed the patients for another 3 months. 10 patients in the recurrent-no-BLIS K12 group had nine episodes of oral streptococcal infection. 15 patients in the recurrent-BLIS K12 group were confirmed to be protected by BLIS K12. Only four episodes of streptococcal infection have been observed during this period which indicates 80% of reduction.

Discussion

Acute pharyngitis accounts for 1%-2% of outpatient visits (8). Group A beta-hemolytic Streptococcus (GABHS) accounts for 20%-30% of cases of acute pharyngitis in children and 5%-15% in adults (8,9). It is more common during winter and early spring (8). Infection can occur in clusters, especially within families, schools, and military settings (9). The prevalence of group A Streptococcus ranges from 4% to 12% in asymptomatic children and 24% to 37% in children with sore throat based on systematic review of 29 prospective studies reporting prevalence of group A Streptococcus from pharyngeal specimens in children ≤ 18 years old (8,9).

Antibiotic therapy is the first line therapy to treat the acute infection and to prevent development of sequelae, such as rheumatic fever. However, sore throat can be caused by a wide range of potential pathogens, including viruses and other bacteria. Usually, antibiotic therapy is useless to treat causes of pharyngitis other than those caused by group A beta-hemolytic streptococci. Inappropriate antibiotic therapy generates unnecessary expense and also contributes to the emergence of antibiotic-resistant bacteria, which is being reported with increasing frequency. Prevention of recurrent infection by non-antibiotic therapy is preferable than having repeated doses of antibiotics. The ability of the normal bacterial microflora in the oral cavity to inhibit the growth of group A streptococci has been established previously (1-5). Mostly, inhibitory activity of normal bacterial flora has been found to be linked to BLIS-producing S. salivarius (4). Since, S. salivarius is a member of the normal bacterial flora found in the oral cavity and is considered to be nonpathogenic, it is thought as a perfect candidate for bacterial interference-mediated prevention of recurrent pharyngitis and tonsillitis (3-5).

It has been shown that S. salivarius K12 inhibits group A streptococcus acquisition and also the prevalence of sore throat (3-5). Therefore, we have decided to use this harmless strain as a prophylactic agent for the feasibility of treating sore throat.

We evaluated the patients if administration of BLIS K12 resulted in durable protection in the months following treatment. This evaluation lasted for 3 months, and showed that prior use of the product provided durable protection against oral streptococcal pathology, with about 80% reduction compared with controls.

This study has several limitations, since it is not randomized nor placebo-controlled, and also was not blinded. However, the results demonstrated that use of S. salivarius K12 can reduce the incidence of bacterial sore throat in patients with a history of recurrent oral streptococcal infection, in spite of these limitations.

Table 1. Demographic characteristics of the patients

Group	n	M	F	Age,yrs*
Recurrent-BLIS	20	11	9	22±4,3
Recurrent-no BLIS	14	7	7	32±3,5
No recurrent-no BLIS	10	6	4	24±5,3
Total	44	24	20	

Expressed as the median±standard deviation. Abbrv: n, number of children; M, males; F, females

Table 2. Episodes of streptococcal oral pathology of BLIS K12 in patients with recurrent streptococcal pharyngitis and/or tonsillitis

	Infection previous year	Infection with BLIS
Incidence	0.29	0.024
Number of Episodes	118	2
Delta		-94.5

Abbrv: BLIS, bacteriocin-like inhibitory substance.

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