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Original Research

Efficacy of administering *Streptococcus salivarius* K12 as a powder formula in preventing respiratory infections in infants

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Abstract

The purpose of this study was to evaluate the efficacy and safety of Bactoblis® as a powder (sachets), containing *Streptococcus salivarius* K12 (minimum 1 billion CFU/sachet) for the prevention of respiratory diseases in young children. This open-label, single-centre, randomized, controlled clinical study was conducted between February 2019 and December 2019 at a Children's Clinical Hospital belonging to the Department of Pediatrics of the Ukrainian Medical and Dental Academy.

Of the 62 children aged six months to two years enrolled, 32 children received a Bactoblis® sachet once daily for 30 days. The children who did not receive Bactoblis® sachets (n=30) served as the control group.

The efficacy of prophylactic administration of Bactoblis® sachets was evaluated in terms of a reduction in the incidence of acute respiratory viral infection (ARVI) episodes, the presence of bacterial complications after a respiratory infection, a need for antibacterial agents and antipyretics and the frequency of visits to an otorhinolaryngologist during the 30-day treatment period and within 90 days of follow-up.

Children treated with Bactoblis® sachets had a significant reduction in the incidence of ARVI episodes compared to those in the control group (p<0.01). The frequency of antipyretic use and otorhinolaryngologist visits was lower in children receiving prophylactic treatment with Bactoblis® sachets compared to the control group (p<0.01).

The incidence of bacterial complications and the requirement for antibacterial agents were reduced in children using Bactoblis® sachets

compared to the control group (p<0.01). No side effects were observed during the study, and 93.8% of patients reported tolerability of the product as excellent.

Our findings indicate that treatment with Bactoblis® in a powder format for 30 days is effective in preventing ARVI episodes in young children (six months to two years). Our results are in line with those reported in previous studies that evaluated Bactoblis® lozenges in children and in adults. This is proposed to be a useful supplementary probiotic for preventing respiratory infections during seasonal diseases and within organized children's communities.

Keywords: Acute respiratory viral infections, Bactoblis®, antibiotic use, pharyngitis, *Streptococcus salivarius* K12

Introduction

Sore throat or pharyngitis is one of the most common symptoms among younger children seeking primary care consultations [1].

Approximately 35% of upper respiratory infections are caused by bacteria, and 65% by respiratory viruses, in paediatric populations [2, 3].

Group A beta-haemolytic *Streptococcus* (GABHS) is a common pathogen causing 80% of bacterial pharyngitis cases in children. It is estimated that there are approximately 616 million new GABHS pharyngitis cases each year globally [4]. Although GABHS pharyngitis may be self-limiting, some patients experience frequent debilitating episodes associated with utilization of health resources and significant economic costs [5].

The annual costs of paediatric GABHS infections were estimated to be between $224 million and $539 million in the United States, which also included indirect costs due to parental work losses [1].

Approximately 53% of children diagnosed with sore throat/pharyngitis are prescribed broad-spectrum antibiotics acutely by their primary care physician, which was found to be more than the maximum expected prevalence rate of GABHS infections, indicating inappropriate prescription of antibiotics [6].

Antibiotics are commonly prescribed to reduce complications related to the infection; however, the incidence of complications related to pharyngitis has been reported to be very low, and therefore, symptom control should be the main goal of treatment of pharyngitis in primary care [7].

This indicates that empirical antimicrobial treatment in children with a sore throat may result in significant overtreatment of non-streptococcal pharyngitis, which may not be cost-effective and poses a risk for antibiotic resistance [8]. Moreover, approximately 50–80% of pharyngitis symptoms have a viral origin and do not respond to antibiotics, and treatment is mainly aimed at relieving symptoms [9]. Given these facts, there is a strong need for alternative prevention and treatment strategies, which could be addressed by the use of probiotics. Probiotics are live, non-pathogenic bacteria

that, when administered in adequate amounts, provide health benefits for the host [10].

The mechanisms underlying these benefits include inhibition of bacterial adhesion and growth, modulation of host immune responses and the production of antiviral agents that inhibit attachment of the virus to the host cell receptor [11, 12]. Current evidence shows that probiotics are effective in preventing episodes of acute upper respiratory tract infection [13].

Streptococcus salivarius K12 (SsK12) is one of the most promising probiotic strains in this regard, with proven efficacy against recurrent streptococcal infection.

Compared to most probiotics targeting the gut, it effectively colonizes the oropharynx and nasopharynx, and produces antimicrobial peptides that belong to Class I lantibiotics (salivaricin A2 and salivaricin B) [14], which inhibit the growth of pathogens that are the main aetiological agents of respiratory infections in children (*S. pyogenes, S. pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*) [15]. Repeated administration of probiotic lozenges containing SsK12 in children above three years of age and in adults resulted in successful colonization of the oral cavity and substantially reduced the incidence of recurrent tonsillopharyngitis and otitis media [5]. This also prevents viral infections most likely by increasing salivary interferon-gamma levels [16].

These findings have led to the use of this probiotic strain not only in children and in adults with recurrent streptococcal pharyngotonsillitis, but also, to prevent respiratory infections of viral aetiology [17].

To date, clinical studies supporting the benefits of SsK12 have been conducted using the lozenge formulation (Bactoblis®), which appeared to be the ideal format ensuring colonization and protection against infection. However, lozenges are not suitable for use in children below three years of age.

Thus, the purpose of this study was to evaluate the efficacy and safety of Bactoblis® as a powder formula (sachets) containing SsK12 (minimum 1 billion CFU/sachet) in combination with fructo-oligosaccharides for the prevention of respiratory diseases in young children (six months to two years). The fructo-oligosaccharides were included to ensure maximum mucosal adhesion and colonization of SsK12 in the oral cavity.

Materials and methods

Study design

This open-label, single-centre, randomized, controlled clinical study was conducted between February 2019 and December 2019 at the Poltava Regional Children's Clinical Hospital of the Department of Pediatrics of the Ukrainian Medical and Dental Academy.

The study period involved 30 days of treatment and a follow-up at 90 days. Hence, the total observation period was 120 days.

This study was conducted following the principles laid down by the Declaration of Helsinki. Local ethics committee approval was obtained (the Commission on Ethics Utility – Poltava Regional Clinical Hospital of the Poltava Regional Council), and parents of the participating children provided signed informed consent.

Patient population

A total of 62 children aged between six months and two years were enrolled in the study. All children were clinically healthy on enrolment. Those with autoimmune diseases, congenital disease of the bronchopulmonary system or abnormalities of the maxillofacial area, immunodeficiencies, concomitant somatic diseases in the stage of decompensation, tuberculosis, those who had episodes of bronchospasm, rheumatic disease or those who received any preventive therapy for recurrent respiratory diseases in the past, were excluded from the study.

Study product

The study product (Bactoblis® sachets, also marketed as Streptoblis®) contained SsK12 (minimum 1 billion CFU/sachet) and 5 µg vitamin D3 in a stable powder matrix of maltodextrin and fructo-oligosaccharides, specifically developed to ensure optimal adhesion of SsK12 to the oral mucosal cells.

The study product has a pleasant strawberry flavour and is packed in an aluminum sachet format to ensure stability. The Bactoblis® sachets were produced according to the standards of GMP, HACCP and ISO 22000, and provided by Bluestone Pharma GmbH.

Study procedure

All children were subject to a general clinical examination and, if necessary, were examined by an otorhinolaryngologist to assess their health status, and were then divided into two groups based on a simple 1:1 randomization key for enrolment. Thirty-two children were prescribed to receive Bactoblis® (in sachets) once daily for 30 days, and 30 children did not receive Bactoblis®, thereby forming the control group. All children (n=62) were given a prophylactic dose of vitamin D3 (400–500 IU). Bactoblis® was administered in the evening before bedtime as per the instructions provided by the manufacturer.

During the entire study period of four months, all parents were requested to bring their child to the clinic as soon as they observed any oropharyngeal symptoms suggestive of an infection. These cases were subjected to a medical examination and a pharyngeal swab test. This rapid test for group A streptococcal antigen is a chromatographic immunological assay for the qualitative detection of streptococcal antigens from throat swab samples to support the diagnosis of group A streptococcal infection.

In cases testing positive, antibiotic treatment (a combination of amoxicillin and clavulanic acid for 10 days) was prescribed to the children.

At the end of the prescribed antibiotic therapy, treatment with Bactoblis® was resumed and continued until the 30th day. In cases of a viral infection accompanied by pharyngolaryngeal pain and/or a fever, the treatment was based on acetaminophen or ibuprofen. Any other pathology was treated according to the local paediatric guidelines.

Study outcomes

The efficacy of prophylactic administration of Bactoblis® was evaluated in terms of reduced incidence of acute respiratory viral infection (ARVI) episodes, the presence of bacterial complications after a respiratory infection, a need to administer antibacterial agents and antipyretics and the frequency of visiting an otorhinolaryngologist (ENT specialist) during treatment with Bactoblis® and in the follow-up period. Diagnosis of ARVI was carried out based on epidemiological history and clinical symptoms, according to the current protocols for the management of children with respiratory infections [18, 19]. Otoscopy and bacteriological studies were performed as needed.

The criteria for prescribing antibacterial drugs were the presence of bacterial complications such as bacterial rhinosinusitis, otitis media and streptococcal tonsillopharyngitis [20].

The incidence of side effects during the entire study period and compliance with the study medication (by counting the number of missed days after taking the drug) were also assessed. Drug tolerance during the trial was assessed subjectively by the patient/parents as being excellent, good or satisfactory.

Statistical analysis

The characteristics of the enrolled children (age, birth weight, feeding of the newborn, ethnicity, attendance at organized children's communities) were assessed using

Fisher's exact test. Differences in the episodes of infection, days of treatment and medication intake were analyzed using the Wilcoxon rank-sum test. The JMP Version 10 software for Mac OS X (SAS Institute, Cary, NC, United States) was used for analysis.

A statistical significance was set at 95%; all *p* values were two-sided, and any *p* value less than 0.05 was considered statistically significant.

Results

Of the 62 children enrolled in the study, 32 received Bactoblis®. The remaining 30 children did not receive any treatment and formed the control group (**Fig. 1**).

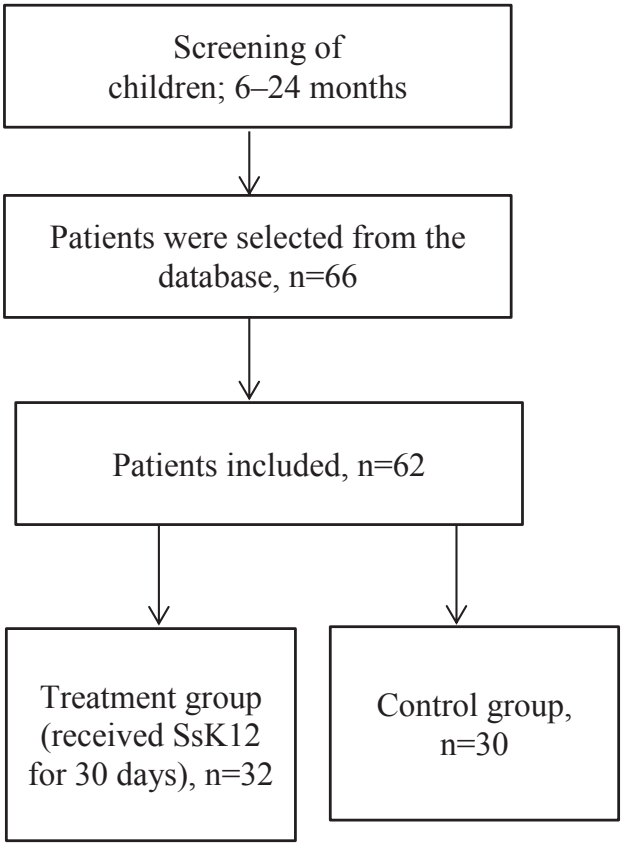

Figure 1 Treatment plan for the patients

The baseline characteristics of the children in the study groups were comparable (**Table 1**).

	Bactoblis® (n=32)	Control (n=30)	*p* value
Average age, months, mean ± SD	17.9 ± 3.2	18.2 ± 2.6	ns
Birth weight, kg, mean ± SD	3.2 ± 0.4	3.3 ± 0.6	ns
Breastfeeding participants	26 (81.3)	25 (83.3)	ns
Formula-feeding participants	6 (18.8)	5 (16.7)	ns
Caucasians	32 (100)	30 (100)	ns
Preschool, community-organized	–	–	–
Participants attending 'home' type of preschool education	32 (100)	30 (100)	ns

Data are shown as n (%) unless otherwise stated; ns = non-significant difference

Table 1 Baseline characteristics of the children included in the study

The children who were treated with Bactoblis® for 30 days had a significant reduction in the incidence of ARVI episodes during the four-month observation period compared to those in the control group ($p<0.01$).

The frequency of antipyretic use and visits to the otorhinolaryngologist were lower in children receiving prophylactic treatment with Bactoblis®, compared to the control group ($p<0.01$).

The incidence of bacterial complications and the requirement for antibacterial agents were lower in children using Bactoblis®, compared to the control group ($p<0.01$) (**Table 2**).

	Bactoblis® (n=32)	Control (n=30)	*p* value
ARVI episodes	12	32	<0.01
Antipyretics, days	14	29	<0.01
Visits to ENT specialists	2	13	<0.01
Bacterial complications, episodes	6	24	<0.01
Administration of antibacterial agents	2	13	<0.01
Antibiotics, days	8	62	<0.01

Data are shown as frequency (n) unless otherwise indicated

Table 2 Clinical characteristics of children during the four-month observation period

The data presented in **Table 3** indicate 'excellent' tolerability and compliance during the study.

Result	Tolerability	Side effects	Compliance
Excellent, n	30	None	26
Good, n	2	None	6
Satisfactory, n	0	None	0

Table 3 Tolerability, side effects and compliance reported in children given Bactoblis® (n=32)

Discussion

Our study demonstrates the efficacy of SsK12 administered in a powder formula (Bactoblis® sachets) in reducing the incidence of ARVI episodes in young children. Our results reiterate the efficacy of this probiotic strain when given in a lozenge formula and showed a reduction in acute upper respiratory tract infections (of bacterial and viral origin), as has been shown in previous studies [5].

Bactoblis® sachets demonstrated good safety, tolerability and compliance, the latter most likely because of the attractive organoleptic properties of Bactoblis® (pleasant taste), which is very important for daily use in children. The main component of our study product, SsK12, has a pronounced antibacterial sensitivity and a robust safety profile [5].

During oral administration, SsK12 colonizes the oral and nasopharyngeal cavity and, in competition with pathogenic microflora, it persists for approximately one month after the last dose has been administered [14, 21]; subsequently, the lantibiotic bacteriocins produced by SsK12 reportedly inhibit not only *S. pyogenes*, but also, other oral bacterial pathogens that cause upper respiratory tract infections, including otitis media [22].

We have previously shown that the administration of Bactoblis® lozenges reduces the colonization of *H. influenzae*, *Staphylococcus aureus* and pneumococcus in the oropharyngeal mucosa. It has been established that Bactoblis® lozenge administration provides benefits for children with recurrent and non-recurrent streptococcal infections, and reduces non-streptococcal infections [23].

The antiviral activity of the lantibiotics may be due to an ability to increase salivary interferon-gamma levels without affecting IL-1β or TNF-α levels, and by substantially lowering IL-8 release that could form a basis for the beneficial effects observed with respect to non-streptococcal infections [16].

The study product also contained vitamin D3, which may have an impact on non-specific and adaptive immune mechanisms [24].

Vitamin D deficiency correlates with dysregulated antigen presentation, and affects the maturation of dendritic cells and Th1 cytokine production. Vitamin D supplementation has been shown to normalize the balance of type 1 and type 2 T helper cytokines and induce the transcription of peptides with a broad spectrum of action against many species of bacteria, viruses and fungi [24].

Hence, the vitamin D3 contained in Bactoblis® may stimulate the phagocytic activity of macrophages, thereby leading to increased production of local IgA antibodies and the amount of lysozyme may optimize specific and non-specific tissue immunity that augments the antibacterial and antiviral activity of SsK12. However, since the children in both groups received a prophylactic dose of vitamin D3 (400–500 IU) a vitamin D3 deficiency in the study population is unlikely. Hence, the impact of the additional vitamin D3 contained in the Bactoblis® sachets on the study outcome is unlikely to be significant.

The clinical efficacy in preventing infections demonstrated in this study correlates with a reduced need for administration of antibacterial agents that are usually prescribed during respiratory infections.

During the 30-day treatment phase and three months of follow-up, SsK12 treatment reduced bacterial complications, antibacterial use, days on antibiotic therapy and visits to ENT specialists in our study.

Several other studies have also shown a reduction in the use of antibiotics in children treated with SsK12 [25, 26]. Antibiotic therapy imposes unnecessary expense and also increases the risk of developing antibiotic resistance, which is a serious emerging issue worldwide. Therefore, a conservative approach of reserving antibiotics for confirmed cases of streptococcal infection is suggested.

Altogether, our study confirms earlier studies reporting clinical benefits of Bactoblis® lozenges in the prevention of respiratory diseases in children and adults [16, 23, 26–30]. Notably, our study is the first of its kind reporting such benefits related to administration of SsK12 in a powder formula to children below three years of age. When evaluating the effectiveness of Bactoblis® sachets in young children, it should be noted that more than 81% of the patients were fully compliant with the regimen in our study. From the present study results we cannot conclude whether there are prolonged benefits beyond the three-month follow-up period. Nevertheless, given the good tolerability of SsK12 and the absence of side effects, it is recommended that children repeat courses two or three times a year to achieve the maximum therapeutic effect.

Conclusions

The findings of this study show that treatment with SsK12 in a mucoadhesive powder formula for 30 days is effective in preventing acute upper respiratory tract infections in children aged six months to two years. Thus, Bactoblis® sachets can be considered an effective supplementary probiotic for children aged six months to two years for restoring the natural microflora after antibiotic therapy, preventing the development of bacterial complications and increasing resistance to viral infections during seasonal diseases and while attending organized children's communities.

Conflict of Interest None

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