Streptococcus Salivarius K12 Probiotic in Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis syndrome

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Abstract: Background and Objectives: Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is the most common syndrome in children. This complication is characterized by the sudden onset of fever, aphthous stomatitis, pharyngitis, and cervical adenitis, as well as less common signs, such as headache, rash, and changes in the digestive system. This study aimed to investigate the effectiveness of the probiotic Streptococcus Salivarius K12 in patients with PFAPA.

Materials and Methods: This randomized clinical trial included PFAPA patients divided into intervention and control groups. The intervention group, along with the conventional treatments, received Lactogum containing Probiotic Streptococcus Salivarius K12 for four months. The control group, however, received conventional treatments, including acetaminophen and non-steroidal anti-inflammatory drugs (prednisolone), along with a placebo.

Results: This study investigated 40 PFAPA patients. The mean ages of the patients in the control and intervention groups were 6.94±2.21 and 5.71±2.59 years, respectively. The highest fever temperature of the children in the control and intervention groups upon admission to the clinic were 38.88±0.53℃ and 39.96±0.85℃, respectively. According to the results, in the first month, the mean number of days suffering from fever was fewer in the intervention group, compared to the control group. Moreover, the mean number of pharyngitis days in the first and second months was fewer in the intervention group than that in the control group. In the fourth month, the disease symptom percentages were reduced in the intervention group, compared to the control group.

Conclusion: The results show that the use of probiotics (Streptococcus Salivarius K12) can be effective in reducing the consumption of corticosteroids and minimizing the complications caused by conventional treatments.

Keywords: Probiotic, PFAPA, Streptococcus Salivarius K12.

1. INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is the most common childhood syndrome (1). This complication is characterized by the sudden onset of fever, aphthous stomatitis, pharyngitis, and cervical adenitis, as well as less common signs, such as headache, rash, and changes in the digestive system (2).

Marshall Syndrome or PFAPA was first described by Marshall in 1987, and it is mainly a disease of children under 5 years of age; however, it has recently been reported in adults. This disease manifests with periodical fevers of about 39˚C at regular intervals (every 3 to 8 weeks) (3). The pathogenesis of PFAPA is unknown; nonetheless, genetic and immunological factors have been implicated in this regard (4). During PFAPA attacks, increased levels of activated T lymphocytes, GM-CSF, G-CSF, and pro-inflammatory cytokines, such as IL-1β, IL-6 and IL-8 have been observed (5).

The fever often increases to 39-40.5˚C, which does not respond to antibiotics and antipyretics. Moreover, more than 90% of children have pharyngitis, followed by up to 75% of cervical adenitis and up to 50% of oral aphthosis during flares. Other symptoms that may present include headache, abdominal pain, arthritis, arthralgia, rash, and diarrhea (6).

PFAPA is diagnosed based on the mentioned criteria, and in addition to the modified Marshall's criteria, other criteria are also defined (4). Currently, the treatments used to improve its symptoms are corticosteroids, nonsteroidal anti-inflammatory drugs (NSAID), colchicine, cimetidine, and tonsillectomy with (ATE) or without (TE) adenoidectomy. The most commonly used first-line treatment in children with PFAPA syndrome is a low-dose corticosteroid, which can improve the symptoms of PFAPA syndrome in 95% of cases. Prednisone is typically given as a single dose of 1-2 mg/kg at the onset of a febrile episode (6).

The evidence indicates that probiotics, especially those containing lactobacilli and bifidobacteria, can be effective and helpful in reducing the occurrence and duration of coughs and colds in children and adults(7). The results of more than 20 studies show that probiotics have reduced the illness duration by about 30%. Bacteriocins Salivaricin A2 and Salivaricin B produced by Streptococcus Salivarius K12 interfere with the growth of Streptococcus pyogenes, Haemophilus influenza D, Streptococcus pneumonia, and Moraxella catarrhalis, which are involved in pharyngotonsillitis and acute otitis media (8).

According to the results of the studies, it is suggested to prescribe Lactocare and KidiLact to adults and children, respectively, to prevent respiratory infections, reduce the risk of other infections, and accelerate the treatment process of these diseases (9, 10). Probiotics can influence the gut microbiome while regulating the immune system. Furthermore, they are effective supplements for preventing or minimizing the immune system's involvement with pathogenic agents that enter the body through the digestive system and for cases, such as allergies or viral-respiratory infections, for which there are generally no specific treatments (6).

Probiotics can exert a protective role in the body; moreover, they prevent the connection of microbial and viral agents and their pathogenicity by fortifying mucosal membranes of the respiratory or digestive tracts and maintaining the integrity of the cells on the surface of these membranes. In addition, probiotics produce antimicrobial substances to destroy pathogens and reduce their number in the body (11).

When pathogenic agents come into contact with the cells of the digestive or respiratory tract wall, they trigger the body's acquired and innate immune systems. Accordingly, probiotics can modulate the immune system's response to these pathogenic agents and reduce their pathogenic and inflammatory effects by strengthening the immune system. Due to their anti-inflammatory effects, probiotics reduce the body's need to use corticosteroid anti-inflammatories, thereby mitigating and ceasing the inflammatory cycles caused by viral and bacterial diseases in the whole body 12).

Pediatric periodical fever symptoms, including aphthous stomatitis, pharyngitis, and adenitis, can cause many complications for children and their families. Since only one study has been conducted so far to investigate the effectiveness of probiotics in preventing and treating this syndrome, this study aimed to evaluate the effect of probiotics on the prevention and treatment of this disease.

2. MATERIALS AND METHODS

This randomized clinical trial was conducted on children diagnosed with PFAPA referred to the Rheumatology and Allergy Clinic of Akbar Children's Hospital, Mashhad, Iran, between September 2021 and September 2022. Written informed consent was obtained from all participants in the study. Patients' demographic characteristics, including age, gender, time of disease diagnosis, and treatments received until entering the study, were recorded. Furthermore, the patients were followed up monthly for four months considering fever episodes, the highest fever temperature, the

number of days suffering from fever, the occurrence of aphthous stomatitis, the presence of pharyngitis and its duration, and the need to use corticosteroids, ibuprofen or acetaminophen.

At the same time, the control group's demographic characteristics and the aforementioned criteria were recorded monthly and were statistically analyzed and compared to those in the intervention group. The inclusion criteria were all patients less than 18 years of age diagnosed with PFAPA based on Marshall's criteria by a pediatric rheumatology subspecialist. On the other hand, the patients whose parents were unwilling to participate in the study and all cases with Overlap Syndrome were excluded from the study. The patients diagnosed with PFAPA based on Marshall's criteria were divided into two groups of intervention and control. In addition to the conventional treatments, the intervention group was requested to suck on Lactogum containing probiotic Streptococcus Salivarius K12 (10^9>CFU) (Zist Takhmir Company, Iran) at night before falling asleep for four months.

On the other hand, the control group received the conventional treatments, including acetaminophen, prednisolone (the standard treatment also included prednisolone [1 mg/kg single dose] during the fever attack and other supportive therapies, including acetaminophen and ibuprofen during fever and pharyngitis), and placebo. The placebo was similar in shape and color to the medications administered to the intervention group and contained a small amount of sugar. The method of its administration was also the same. Furthermore, the prednisolone dose was the same in both groups. In this triple-blind study, the blinding was extended to the subjects, evaluators, and analysts. The simple randomization method was used to generate a random allocation sequence using *sealedenvelop.com*, and the allocation concealment method was opaque, sealed, closed, and numbered envelopes.

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IRMUMSMEDICALREC.1400.408), and it has also been registered in IRCT (trial registration number: IRCT20210911052436N1).

3. RESULTS

This clinical trial investigated 40 patients diagnosed with PFAPA based on Marshall's criteria and assigned to control (n=26) and intervention groups (n=14). The mean ages of the patients in the control and intervention groups were 6.94±2.21 and 5.71±2.59 years, respectively. The highest fever temperature of children upon admission to the clinic was 38.88˚C in the control group and 39.96˚C in the intervention group. The mean weight values of the control and intervention groups were 24.42±8.83 and 17.87±5.13 kg, respectively. The mean±SD of the quantitative variables are reported in Table 1 by month.

Table 1: Quantitative variables in the control and intervention groups during four months

Month	Variable	Control group N=26			Intervention group N=14			*P*- value
		Mean±SD	Min	Max	Mean±SD	Min	Max	
Upon admission	**Highest fever temperature (°C)**	38.88±0.53	38.0	40.0	39.96±0.85	38.5	0.41	0.001>
First month	**Duration of fever (days)**	2.69±0.67	2	4	3.46±3.40	0	10	0.777
	Highest fever temperature (°C)	38.88±0.53	38.0	40.0	39.40±0.93	38.0	0.41	0.060
	Duration of pharyngitis (days)	2.31±0.73	1	5	2.10±3.10	0	10	0.279
Second month	**Duration of fever (days)**	2.15±0.61	1	3	1.92±3.32	0	10	0.032
	Highest fever temperature (°C)	38.51±0.51	38.0	40.0	40.10±0.65	39.5	41.0	0.001
	Duration of pharyngitis (days)	1.88±0.58	0	3	1.50±2.93	0	10	0.031
	Duration of fever (days)	1.40±1.08	0	3	2.46±3.01	0	10	0.580

Month	Variable	Control group N=26			Intervention group N=14			*P*- value
		Mean±SD	Min	Max	Mean±SD	Min	Max	
Third month	**Highest fever temperature (°C)**	38.55±0.45	38.0	39.0	39.42±0.44	39.0	40.0	0.001
	Duration of pharyngitis (days)	1.04±1.02	0	3	1.69±2.95	0	10	0.755
Fourth month	**Duration of fever (days)**	1.38±1.06	0	3	2.08±1.89	0	5	0.276
	Highest fever temperature (°C)	38.44±0.43	38.0	39.0	39.75±1.03	38.5	42.0	0.001**>**
	Duration of pharyngitis (days)	0.96±0.82	0	2	1.15±1.67	0	5	0.728

* Mann-Whitney test was used to analyze qualitative variables.

Figure 1 compares the mean fever duration in the control and intervention groups during four months of visiting the clinic.

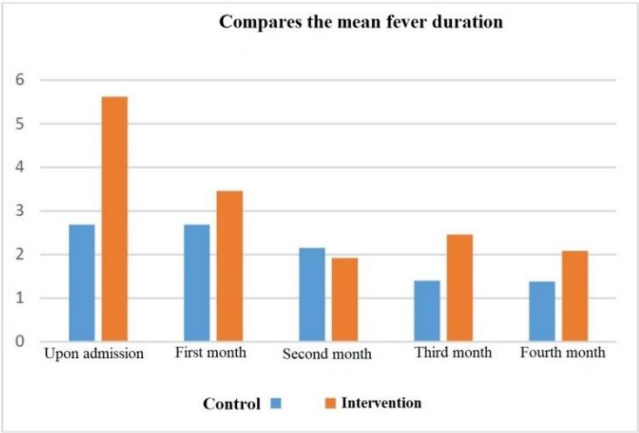

Figure 1: Comparison of the control and intervention groups regarding fever duration during four months

Mean pharyngitis duration is also compared in two control and intervention groups during four months of visiting the clinic (Figure 2).

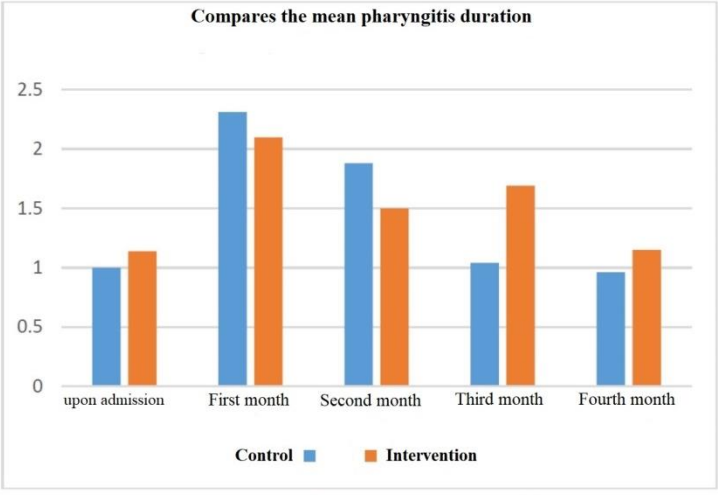

Figure 2: Comparison of the control and intervention groups regarding pharyngitis duration during four months

Table 2 tabulates the frequency and frequency percentage of qualitative variables in two control and intervention groups upon admission to the clinic. Based on the statistical analysis of the qualitative variables at the beginning of the study, it can be concluded that there is a significant difference between the intervention and control groups regarding the number of days suffering from fever per month, the duration of pharyngitis per month, the presence of cervical adenitis, and the use or non-use of corticosteroids ($P \leq 0.05$).

According to the examination upon admission, 23.1% and 28.6% of the patients in the control and intervention groups had comorbidities, respectively. Moreover, 80.8% and 88.9% of the patients in the control and intervention groups lived in the city. In addition, 53.8% and 38.5% of the patients in the control and intervention groups had aphthous stomatitis, respectively. All patients in the control group and 85.7% of the cases in the intervention group suffered from pharyngitis. In total, 74.4% of the participants had cervical adenitis (control group=96.2%, intervention group=30.8%). All patients in the control group (n=26) consumed corticosteroids (prednisolone); however, 42.9% of the cases in the intervention group used this medication. In addition, 65.4% and 61.5% of the cases in the control and intervention groups used ibuprofen, respectively, and both groups consumed acetaminophen.

Table 2: Relationship between the number of days suffering from fever and the pharyngitis duration per month in two control and intervention groups upon admission

Variable		Control group N (%)	Intervention group N (%)	Total N (%)	*P*-value
Number of days suffering from fever per month	2 days	11(42.3)	0(0.0)	11(28.2)	0.001**>**
	3 days	12(46.2)	2(15.4)	14(35.9)	
	4 days	3(11.5)	2(15.4)	5(12.8)	
	5 days	0(0.0)	4(30.8)	4(10.3)	
	6 days	0(0.0)	2(15.4)	2(5.1)	
	7 days	0(0.0)	1(7.7)	1(2.6)	
	10 days	0(0.0)	2(15.4)	2(5.1)	
	Total	26(100.0)	13(100.0)	39(100.0)	
	No fever	0(0.0)	2(14.3)	2(5.0)	
	Total	26(100.0)	14(100.0)	40(100.0)	
Pharyngitis duration per month	0 day	0(0.0)	2(22.2)	2(5.7)	0.014
	1 day	1(3.8)	0(0.0)	1(2.9)	
	2 days	18(69.2)	2(22.2)	20(57.1)	
	3 days	6(23.1)	2(22.2)	8(22.9)	
	5 days	1(3.8)	2(22.2)	3(8.6)	
	10 days	0(0.0)	1(11.1)	1(2.9)	
	Total	26(100.0)	9(100.0)	35(100.0)	

*** Chi-square test was used to analyze qualitative variables**

The frequency, frequency percentage, and correlation of qualitative variables in two control and intervention groups were investigated at the first, second, third, and fourth months of the patients' visits. The statistical analysis of the Chi-square test shows a significant difference between the intervention and control groups in terms of all qualitative variables, including fever, aphthous stomatitis, pharyngitis, and cervical adenitis, at the first month of administering Lactogum ($P \leq 0.05$).

There was also a significant difference between the two groups in terms of the use of acetaminophen ($P=0.035$), ibuprofen ($P=0.006$), as well as cimetidine and famotidine ($P=0.060$). The results of the Chi-square test reveal a

significant difference between the intervention and control groups regarding all qualitative variables in the second month, except for the use of ibuprofen, cimetidine, and famotidine ($P \leq 0.05$).

According to the statistical analysis, only cervical adenitis showed a significant difference in the intervention and control groups in the third month after the onset of treatment ($P \leq 0.05$). There was also a significant difference between the intervention and control groups in terms of cervical adenitis and corticosteroid use in the fourth month after the onset of Lactogum treatment ($P \geq 0.05$). According to the mentioned results, Figure 3 illustrates the percentage of aphthous stomatitis in the patients of the control and intervention groups during four months of visiting the clinic.

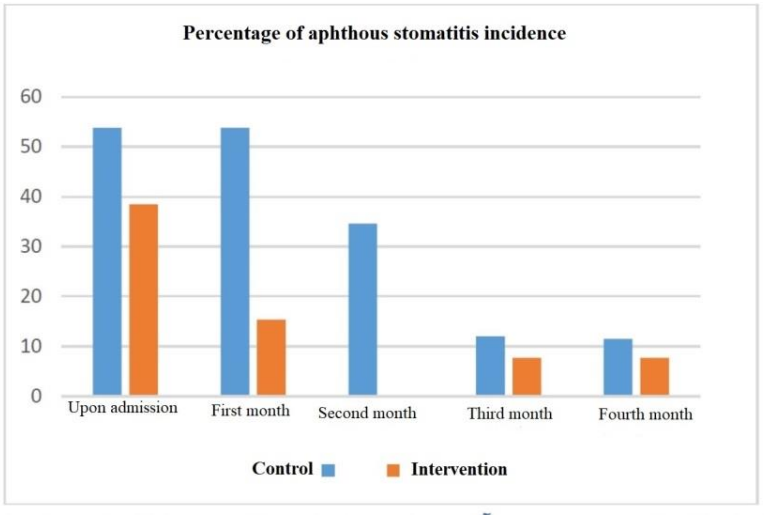

Figure 3: Comparison of the control and intervention groups regarding the incidence of aphthous stomatitis during four months

The corticosteroid use percentage in the control and intervention groups during four months of visiting the clinic is shown in Figure 4.

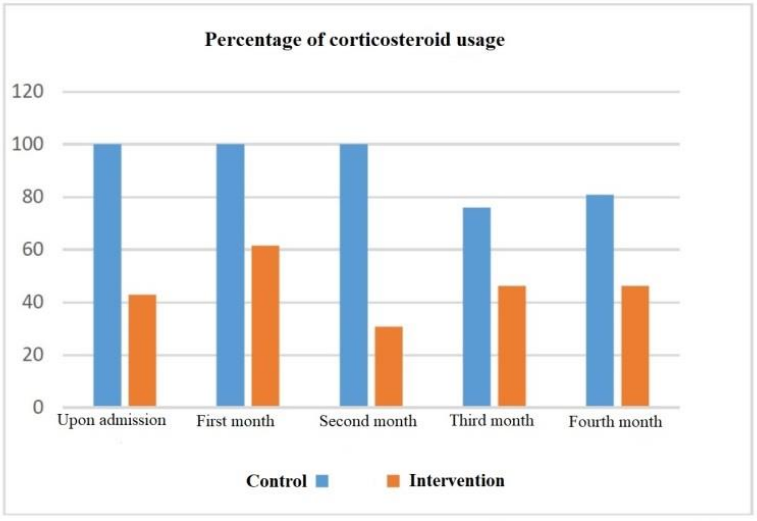

Figure 4: Comparison of the control and intervention groups regarding corticosteroid use percentage during four months

4. DISCUSSION

Childhood periodical fever with aphthous stomatitis, pharyngitis, and adenitis can cause many complications for children and families. Nowadays, probiotics are used to prevent and help treat many diseases. This study mainly aimed to investigate the effectiveness of the probiotic Streptococcus Salivarius K12 in the treatment of patients with PFAPA. This clinical trial included 40 patients diagnosed with PFAPA based on Marshall's criteria assigned into

control (n=26) and intervention groups (n=14). The mean ages of the patients in the control and intervention groups were 6.94±2.21 and 5.71±2.59 years, respectively. The highest fever temperature upon admission to the clinic was 38.88±0.53˚C in the control group and 39.96±0.85˚C in the intervention group. The mean weight values in the control and intervention groups were obtained at 24.42±8.83 and 17.87±5.13 kg, respectively.

Statistical analysis shows no significant difference between the intervention (received Lactogum) and control groups regarding age (P=0.205), the number of days suffering from fever in the first month (P=0.777), the highest fever temperature in the first month (P=0.060), the number of days suffering from pharyngitis in the first month (P=0.279), the number of days suffering from fever in the third month (P=0.580), the number of days suffering from pharyngitis in the third month (P=0.755), the number of days suffering from fever in the fourth month (P=0.276)), and the number of days suffering from pharyngitis in the fourth month (P=0.728).

However, according to the results, there is a significant difference between the intervention (received Lactogum) and control groups regarding weight (P=0.012), highest fever temperature upon admission (P=0.00), the number of days suffering from fever in the second month (P=0.032), highest fever temperature in the second month (P=0.001), the number of days suffering from pharyngitis in the second month (P=0.031), the highest fever temperature in the third month (P=0.001), and the highest fever temperature in the fourth month (P=0.00).

Based on the analysis of quantitative variables, the mean number of days suffering from fever in the first month of the study was fewer in the intervention group, compared to the control group. Additionally, the mean number of days suffering from pharyngitis was fewer in the first and second months in the intervention group, compared to the control group**.** Furthermore, statistical analysis of the qualitative variables upon the patient's admission to the clinic indicated a significant difference between the intervention and control groups in terms of the number of days suffering from fever per month, the pharyngitis duration per month, the presence of cervical adenitis, and the use or non-use of corticosteroids (P≥0.05).

The results of the Chi-square test also revealed a significant difference between the intervention and control groups in terms of all qualitative variables in the first month after the onset of Lactogum treatment (P≥0.05). Moreover, all qualitative variables in the second month showed a significant difference between the intervention and control groups, except for the use of ibuprofen, cimetidine, and famotidine (P≥0.05).

In the third month, only the existence of cervical adenitis after the onset of treatment in the intervention and the control groups showed a significant difference (P≥0.05). In the fourth month after the onset of Lactogum treatment, a significant difference was observed between the intervention and control groups regarding cervical adenitis and corticosteroid use (P≥0.05).

The results of this study showed a reduction in the disease symptom percentages in the intervention group, compared to the control group, during four consecutive months of referring the clinic. In a study by Francesco Di Pierro et al. on adults, probiotic Streptococcus Salivarius K12 reduced the episodes of tonsillitis and pharyngitis caused by Streptococcus pyogenes by approximately 90% (13).

In another study, episodes of pharyngitis, streptococcal tonsillitis, and acute otitis media were reduced in 41 children with frequent oral streptococcal infection treated with Streptococcus Salivarius K12 prophylaxis for 90 days (14). In the same line, Giuseppe Gregori et al. considered prophylaxis with oral probiotic Streptococcus Salivarius K12 as a factor in reducing the episodes of group A beta-hemolytic streptococcal pharyngotonsillitis. They suggested this medication instead of prescribing antibiotics to these patients (15).

In one study, PFAPA patients treated with Streptococcus Salivarius K12 for 90 days showed a reduction in symptoms and medication use (16). Furthermore, the probiotic Streptococcus Salivarius K12 was used in a study for over three months by four PFAPA patients, and the results revealed reduced levels of pharyngotonsillitis and acute otitis media. Additionally, three cases were without symptoms and reported a better quality of life (2, 17).

According to the results of this study, owing to the effectiveness of this treatment and since probiotics have no side effects, they can mitigate complications caused by conventional treatments (especially corticosteroid treatment). Furthermore, the probiotic Streptococcus Salivarius K12 can be used in patients with PFAPA to minimize symptoms, thereby reducing the need to administer other medications to these patients.

5. CONCLUSION

This study aimed to investigate the effect of probiotics (Streptococcus Salivarius K12) in the form of Lactogum tablets (Zist Takhmir Company, Iran) along with conventional treatments on children suffering from periodic fever with aphthous stomatitis, pharyngitis, and adenitis. This disease is the most common syndrome in childhood. Probiotics and vitamin D are among the treatments that have been recently suggested to reduce the episodes in these patients and make them asymptomatic. Probiotics can stimulate and strengthen the immune system and reduce the possibility of the recurrence of infection and the recovery period of infectious diseases. Corticosteroids' side effects can be prevented by the use of probiotics. According to the results of this study, the use of probiotics (Streptococcus Salivarius K12) can be effective in reducing the symptoms and episodes of the disease, as well as the consumption of corticosteroids. Therefore, due to no side effects in the use of probiotics and the effectiveness of this treatment, the complications caused by conventional treatments (especially corticosteroid therapy) can be significantly reduced.

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