SOMATO PUBLICATIONS

Annals of Dental Science and Oral Biology

Research Article

Results of Clinical Observation to Assess the Impact of Infanetim Technology Black Line Toothpaste on the Risk of Influenza and Arvi in Adults (Black-1)

Shimansky Shalva Levanovich[1] and Shabalkin Pavel Igorevich[2*]

[1]FGBU, Moscow State Medical University of A.I. Evdokimov, Ministry of Health of Russia, st. Delegatskaya, 20/1, 127473, Moscow, Russia

[2]Clinic of Oncoimmunology and Cytokine Therapy, , St. Stroitelej 7/1, 119311, Moscow, Russia

*Address for Correspondence: Shabalkin Pavel Igorevich, Clinic of Oncoimmunology and Cytokine Therapy, , St. Stroitelej 7/1, 119311, Moscow, Russia, E-Mail: p.shabalkin@gmail.com

Received: 13 September 2021; Accepted: 20 October 2021; Published: 23 October 2021

Citation of this article: Shimansky, SL., Shabalkin, PI. (2021) Results of Clinical Observation to Assess the Impact of Infanetim Technology Black Line Toothpaste on the Risk of Influenza and Arvi in Adults (Black-1). Ann Dent Sci Oral Biol, 2(1): 01-08.

Abstract

Aim: To assess the effect of daily use of INFANETIM Technology Black line hygienic toothpaste in adults on the risk of incidence of influenza and ARVI.

Patients and methods: We conducted a controlled clinical observation BLACK-1 with the participation of volunteers over 18 years old to evaluate the effectiveness of INFANETIM Technology Black line hygienic toothpaste for reducing the incidence of SARS and influenza during November 2019 - March 2020. The observation was carried out on the basis of the dental clinic A.I. Evdokimov Moscow State Medical University of the Ministry of Health of Russia and the Clinic of Oncoimmunology and Cytokine Therapy LLC. 2,000 volunteers were randomly assigned to use either the INFANETIM Technology Black line hygienic toothpaste, or the generic hygienic toothpaste daily for about 2 months. Researchers received weekly remote information on the health status of the volunteer to track cases of respiratory diseases and their outcomes.

Results: During the 8-week period, the incidence rate per 2,000 people was 70 in the INFANETIM Technology group (vs. 344 in the control group, p-value = 0.040; 95% CI 22-32%). The incidence of laboratory-confirmed influenza was 31% lower in the study group (23/70) than in the control group (220/344) (P-value = 0.012; 95% CI 25-37%). In the study group, only 3 cases of hospitalization due to the development of bacterial pneumonia were registered; in the control group, complications were

described in 116 participants.

Conclusions: Daily oral hygiene using specialized toothpastes such as INFANETIM Technology Black line, which can provide an additional barrier to the penetration of viral and bacterial infections, reliably reduces the incidence of respiratory viral infections and reduces the risk of complications, also in the form of bacterial pneumonia.

Key words: Influenza, ARVI, INFANETIM Technology Black line toothpaste.

Introduction

Influenza is an acute highly contagious respiratory viral disease with a short incubation period, caused by influenza viruses, transmitted via airborne droplets. The disease quickly and cyclically affects the epithelium of the mucous membrane, mainly of the upper respiratory tract, accompanied by intoxication and catarrhal syndrome. There are three types of seasonal influenza viruses: A, B and C (family Orthomyxoviridae, genus Influenzavirus). Human influenza A and B viruses cause seasonal epidemics almost every winter. Influenza C causes mild respiratory illness and is much less common than A and B. Influenza A viruses are further classified into subtypes according to the different types and combinations of the virus surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA) [1,2].

Flu symptoms include fever, myalgia, headache, sore throat, cough, chills, nasal congestion [3].

Influenza is known to be dangerous with complications. In the epidemic season, the risk of developing bacterial infections caused by staphylococcus aureus, streptococci and chlamydia increases, occurring in a severe and rapidly progressive form [4].

The severe course of a viral disease is accompanied by damage to the lower respiratory tract or the entire respiratory tract with respiratory failure, pulmonary edema, otitis media, vascular collapse, lesions of the central nervous, urinary system and gastrointestinal tract, the development of secondary bacterial infections [1,2].

Secondary bacterial pneumonia is the most common complication of influenza [3].

Influenza-like illness (ILI) is understood as a clinical case characterized by an acute onset of the disease in the form of a high temperature above 38° C, cough or sore throat, with lack of a different diagnosis. In addition, ILI may be accompanied by other symptoms, including headache, fatigue, runny or nasal congestion, body aches, diarrhea, and vomiting [4].

According to "Federal State Statistics Service of the Russian Federation"estimates, during the 2019–2020 influenza season, the mortality rate ranged from 12,000 to 56,000 people, and the hospitalization rate - from 140,000 to 710,000.

According to the WHO, annually up to 650 thousand people die from respiratory diseases associated with seasonal flu. This indicator is calculated on the basis of the latest global data without taking into consideration deaths for other reasons and suggests the need to search for new methods of preventing seasonal epidemics [5].

Preventive measures to combat influenza and ARVI viruses can be specific and nonspecific and should be aimed at the following elements: the source of the infection, the routes of transmission and the susceptibility of the host organism [1].

Vaccination is a specific method of prevention. The main disadvantage of this method is that the effectiveness of influenza vaccines varies significantly from year to year, as it is largely determined by the coincidence between the vaccine strains and the viruses circulating during the season. In addition, the effectiveness of vaccinations may be lower among people with chronic diseases, among the elderly, as well as in persons with immunodeficiency states, compared with healthy young people due to the lack of their own immune defense. In the Russian Federation, about half of the population suffers from secondary immunodeficien-

cies, which contribute to the more frequent development of ARVI, which in turn aggravates the patient's condition in terms of the immune system [6,2].

It is assumed that non-specific preventive measures aimed at the source of infection and the route of its transmission, can be effective tools for combating infectious diseases. Thus, regular hand washing, rinsing the exterior parts of the nasal cavity with special solutions and protecting the respiratory tract with a disposable mask, changable every 2 hours, for example, according to studies, can reduce the frequency of infections. However, the practice of frequent hand washing and nasal hygiene using soap and water is not always available and often difficult, as is the frequent change of disposable masks. At the same time, alternative personal hygiene products, such as toothpaste, which has a long-term 12-hour immunoactive antiviral and antibacterial effect, can be a good addition to a comprehensive non-specific prevention program, improve the epidemiological situation and, as a result, reduce the risk of infection with influenza and ARVI viruses [2].

The long-term combined effect of INFANETIM Technology toothpaste is mediated by the introduction of a thermostable composition, which consists of two bioactive components that stimulate natural antiviral immunity and help the body overcome infectious diseases on its own. Thus, providing antibacterial protection and inhibiting the growth of pathogenic bacteria. This is a new product on the market that has no analogues.

According to the results of studies of biological activity, the thermostable composition showed antiviral properties, expressed in an increase in the resistance of cells to the action of the vesicular stomatitis virus compared to placebo with prolonged exposure (within 24 hours). The thermostable composition of biologically active substances is a patented component of this toothpaste [8]. Its antiviral and antibacterial effect is due to the presence of the minimum permissible concentration of biologically active substances, based on the recombinant proteins interferon gamma and lysostaphin.

Antimicrobial activity tests have also been performed. A 5-fold bacteriolytic activity of the thermostable composition was observed against the test strains of *St.aureus* and *St.Epidermidis* (vs. placebo). Upon further observation, inhibition of bacterial cell growth on the plates was noted within 24 hours compared to 4 hours for placebo.

The hypothesis of the study is based on the fact that with the regular use of a paste containing the minimum permissible concentration of interferon gamma and the bactericidal enzyme lysostaphin, a preventive local effect is achieved that activates the immune response. And the effect of lysostaphin provides a bactericidal effect.

Objectives

The main goal of clinical observation was to assess the effect of daily use of INFANETIM Technology Black line hygienic toothpaste in adult volunteers on the risk of influenza and ARVI.

The primary observation result was the incidence of influenza or ARVI (influenza-like illness) among adults using INFANETIM Technology Black line hygiene paste, compared with a control group of adults using other brands of hygiene paste.

The secondary outcome was the number of cases of complications of influenza in the form of bacterial pneumonia and / or hospitalization due to the development of influenza-like illness.

Patients and methods

We conducted a prospective controlled clinical observation BLACK-1 with the participation of volunteers over 18 years old to evaluate the effectiveness of INFANETIM Technology Black line hygienic toothpaste for reducing the incidence of SARS and influenza during the period of November 2019 to February 2020. SARS was not separately included in the analysis due to the fact that the study was started in the 2019 season, at that time there were no officially recorded cases of SARS, and there was no system test for its diagnosis.

Research sites

The observation was carried out on the basis of:

1) Dental clinic "A.I.Evdokimov Moscow State Medical University " of the Ministry of Health of Russia;

2) Clinic of Oncoimmunology and Cytokine Therapy LLC.

Randomization

2,000 volunteers were randomly assigned in a 1:1 ratio into 2 groups to apply either the INFANETIM Technology Black line hygienic toothpaste, or a generic hygienic toothpaste, which were used daily for about 2 months. The randomization was done in a simple manner using envelopes. The randomization list was prepared by a biostatistician. No masking was intended.

Participants

The volunteers participating in this clinical observation were persons over 18 years of age without clinical symptoms of acute diseases, who considered themselves healthy, in the absence of confirmation from the results of laboratory and other examinations. The presence of chronic concomitant pathologies in the compensation phase was allowed, as well as the use of concomitant therapy.

Each participant in the program BLACK-1 was previously informed of the goals and procedures of clinical observation with the voluntary receipt of written informed consent for the collection and processing of medical data. With regard to the personal data of the participants, the confidentiality policy, appropriate by the legislation of the Russian Federation, was followed.

Female volunteers who were pregnant or breastfeeding were not allowed. All female volunteers of reproductive age with preserved reproductive function were obliged to follow reliable methods of contraception (double barrier) and to inform the researchers about the fact of pregnancy during the clinical observation program or within the next 3 months after its completion.

Volunteers with individual intolerance to the ingredients of the test product were not allowed.

Investigational product

The INFANETIM Technology Black line hygienic toothpaste was used by 1,000 volunteers from the study group. The duration of use and clinical observation were carried out over the period of approximately 2 months.

INFANETIM Technology toothpaste effectively removes plaque, leaves a feeling of freshness in the oral cavity, preserves and restores the integrity of the tooth enamel. An additional advantage of the INFANETIM Technology Black line hygienic toothpaste is the presence of a thermostable composition. The original composition of the thermostable composition with biologically active substances reduces the risk of developing inflammatory processes in the oral cavity, and also provides an additional barrier to the penetration of bacterial and viral infections.

Control product

Any other hygienic paste for daily use was applied by 1,000 volunteers in a control group. The observation was carried out over the period of approximately 2 months.

Criteria for evaluation

All cases of ILI were registered with the confirmation by reverse transcription polymerase chain reaction (RT-PCR) or clinical examination within 3 days of the onset of symptoms of the disease; all cases of complications in the form of bacterial pneumonia and hospitalization for a reason associated with the development of the disease.

Measurements and procedures

During the first visit, a volunteer received full information about the clinical observation program BLACK-1 and signed an informed consent form. On the same day, demographic data, medical and allergy history were recorded, and a diary was handed out to keep records of the brushing procedure. The study product - INFANETIM Technology Black line toothpaste - was handed out given that the volunteer was randomly assigned to the study group.

Volunteers in both groups were required to brush their teeth 2 times a day (morning and evening) according to the recommendation of a dentist brushing teeth with the prescribed toothpaste for at least three minutes. The time and duration of brushing was noted daily by a volunteer in a specialized diary. At the end of the study, adherence to the daily routine was assessed based on the data recorded by the volunteer in the diary.

Researchers received weekly over-the-phone information on the health status of a clinical observation participant to track ILI cases, as well as collected data on probable contacts with ILI patients and

visits to unfavorable public places as for influenza epidemiology. The observation period for each participant was about 2 months. If information was found about contact with a patient with ILI, or about visits to places that are epidemiologically unfavorable, the observation period continued for at least 7 days after the set date, even if the planned period of participation of the volunteer was completed. During the additional follow-up period, the participant continued to use the prescribed hygienic toothpaste whenever possible. Chemoprophylaxis was not prohibited.

When an episode of the illness was detected, the patient was invited for a visit to collect samples of nasal and nasopharyngeal discharge for testing for viruses during the first 3 days from the moment of clinical manifestation of the disease (before the start of antiviral therapy), clarifying the symptoms of the disease and conducting an objective examination.

Samples were taken from the depths of the nasal passages (with a nasal swab) or from the nasopharynx (with a nasopharyngeal swab).

Samples from patients with ILI were examined by RT-PCR for the presence of influenza A (H1N1), A (H3N2), A (H5N1) and B viruses, as well as parainfluenza, adeno- and respiratory syncytial viruses.

The patient's treatment was prescribed and monitored by the attending local physician. For participants who became ill during the follow-up period, additional information was collected on cases of pneumonia and / or hospitalizations associated with the progression of ILI. These clinical cases were observed until their complete resolution.

The assessment of the volunteers' adherence to compliance with the rules for the use of toothpaste (brushing their teeth 2 times a day - in the morning and in the evening - for at least 3 minutes) was carried out on the basis of the participant's entries in a specialized diary. The diary was issued on the first day of participation: after signing informed consent, randomization and inclusion in the clinical observation program.

At the last visit (after 2 months ±7 days from the start of the toothpaste application), the diary was returned with the used tubes of toothpaste. In the case of the patient's adherence to the use of toothpaste of less than 75% (to discern whether the procedure of brushing the teeth was carried out irregularly – for instance with gaps more than 30 applications, or with another paste - the filling of the returned tubes was assessed), the participant was excluded from the observation program and was not taken into account when processing the results.

Statistical analysis

Statistical analyses were performed using R (v3.5.1). Qualitative variables were compared by Fisher exact test, and quantitative variables by Wilcoxon rank sum test. All tests were two-sided. Statistical significance was set at $p < 0.05$.

Results

The observation program BLACK-1 included 2,000 volunteers. All volunteers were randomly assigned into 2 groups in a 1: 1 ratio (1000 people each) and underwent a full observation program for a period of approximately 2 months. There were no participants who left early, including because of withdrawal of informed consent or lack of adherence to the study method. There were deviations from the program associated with the timing of the visit due to the occurrence of a clinical case: sampling for RT-PCR studies in 116 participants was performed later (4-6 days from the onset of symptoms of the disease). Table 1 presents data on baseline characteristics of participants, Table 2 presents data on comorbidities of participants. Table 3 summarizes the additional preventive measures used by the participants to reduce the risk of ILI.

For all of the above baseline parameters, the two groups of volunteers were comparable to each other.

Among the hygienic toothpastes used by members of the control group, the most popular brands were (%): R.O.C.S. (57), Sensodyne (18), Colgate (13), Splat (5), Biomed (3), Forest Balsam (1), ApaCare (1), Bluem (1), Periodontol (1).

70 volunteers who used the study product during the entire clinical observation (about 2 months) developed ILI. 33% (23 people) of them had a confirmed RT-PCR infection with the influenza A virus. The H1N1 variant was detected in 20 people and the H3N2 variant - in 3 of the participants. In the control group of 344 pa-

Table 1: Baseline characteristics of participants

Parameter	INFANETIM Technology Black line toothpaste, n=1,000	Other toothpaste brand, n=1,000
Age, M±SD (years)	49±6.2	42±8.2
Female, %	39	35
Male, %	61	65
Current positive vaccination status, %	41	46
Current negative vaccination status, %	59	54
Presence of concomitant diseases, %	63	49

Table 2: Comparative characteristics of groups for concomitant diseases

Concomitant pathology	INFANETIM Technology Black line toothpaste, n=1,000	Other toothpaste brand, n=1,000
Chronic heart diseases, %	10	15
Chronic pulmonary diseases, %	13	10
Metabolic syndrome, %	26	25
Other, %	87	69

Table 3: Comparative characteristics of groups on the use of additional preventive measures

Preventive measure	INFANETIM Technology Black line toothpaste, n=1,000	Other toothpaste brand, n=1,000
Masks, %	27	33
Healthy lifestyle, %	29	36
Chemoprophylaxis, %	90	73

tients with ILI, the majority of patients - 64% (220 people) - were infected with influenza A and B (190 and 30, respectively) viruses. Among type A viruses, the H1N1 variant prevailed (158 cases), the remaining 32 cases were due to the H3N2 variant.

Among ARVI (47 in the study group vs. 124 in the control group), adenoviruses were regularly detected (30/47 versus 96/124, respectively), isolated cases of parainfluenza (3 in the study group and 16 in the control group) and infections caused by respiratory syncytial virus (14 in the study group and 12 in the control group) were recorded (Figure 1). Comparative characteristics of the incidence of participants in both groups.

Table 4 presents the summary results of clinical observation evaluating the number of ILI cases in both groups.

Thus, during the 8-week clinical follow-up period, the incidence of influenza-like illness per 2,000 people was 70 in the INFANETIM Technology group and 344 in the control group (p-value = 0.040; 95% CI 22-32%). The incidence of laboratory-confirmed influenza was 31% lower in the study group (23/70) than in the control group (220/344) (P-value = 0.012; 95% CI 25-37%).

There was also a significant difference (p-value = 0.002; 95% CI 27-31%) between the incidence of complications in the study group (3 cases out of 70 cases) and in the control group (116 cases out of 344 cases) based on the results of the subsequent clinical follow-up of affected participants. In 90 control participants with complicated cases of ILI, the established diagnosis of bacterial pneumonia was confirmed, 26 were hospitalized for inpatient treatment. No fatal cases were registered.

Table 4: Results of clinical observation on the distribution of ILI cases

Diagnosis	INFANETIM Technology Black line toothpaste, n=1,000	Other toothpaste brand, n=1,000	p-value
Influenza A(H1N1)	20	158	0,070
Influenza A(H3N2)	3	32	0,285
Influenza B	0	30	0,528
Total (Influenza)	23	220	0,012*
Parainfluenza	3	16	0,540
Adenovirus	30	96	0,600
Respiratory syncytical virus	14	12	0,122
Total	70	344	0,040*

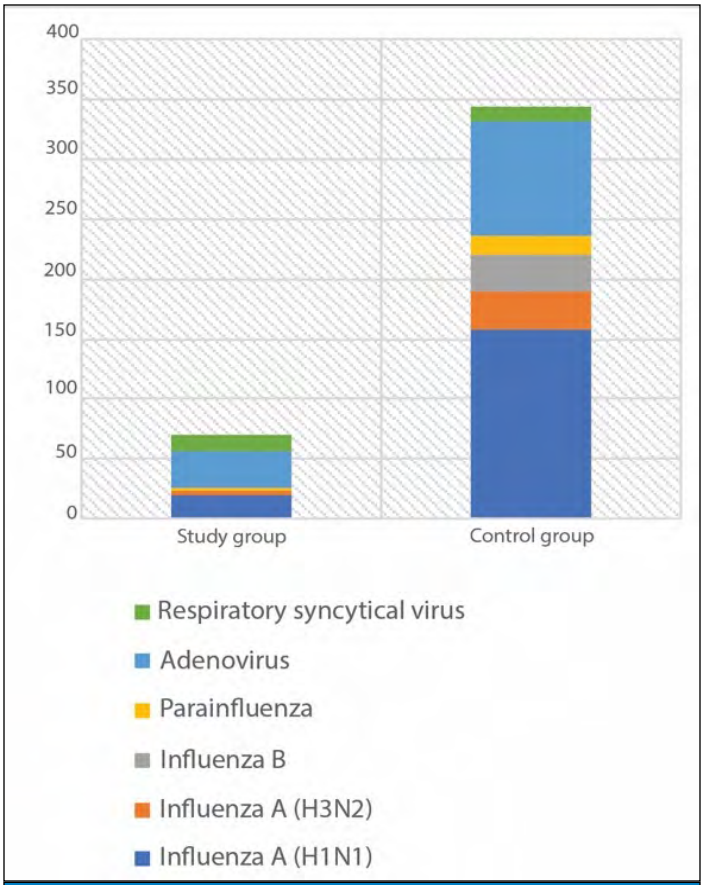

Figure 1: Comparative characteristics of the incidence of participants in both groups

Based on the results of clinical observation, it was concluded that the use of INFANETIM Technology Black line hygienic toothpaste 2 times a day reduces the incidence of ARVI and influenza.

Discussion

The results of clinical testing BLACK-1 showed that oral hygiene using INFANETIM Technology Black line toothpaste can significantly reduce the risk of respiratory tract infections. At the same time, the frequency of laboratory confirmations of influenza among sick patients also significantly decreases by almost a third - 31% (95% CI 25-37%). This indicates a high prophylactic activity of the product against influenza and ARVI viruses, at least those strains that circulated in the Russian Federation during the 2019/2020 epidemiological season.

Conclusions

Daily oral hygiene using specialized toothpastes such as INFANETIM Technology Black line, which can provide an additional barrier to the penetration of viral and bacterial infections, reliably reduces the incidence of influenza-like diseases and reduces the risk of complications, including bacterial pneumonia.

Main source of funding

The clinical observation program BLACK-1 was supported by the Clinic of ImmunoOncology LLC.

References

1. Influenza in adults: guidelines for diagnosis, treatment, specific and non-specific prevention / A.G. Chuchalin, T.V. Sologub. SPb, 2014.
2. Eliakim-Raz, N., Vinograd, I., Trestioreanu, AZ., Leibovici, L., Paul, M. (2013) Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev, 2013(10): CD008983.

3. Kamps, BS., Homann, C., Preiser, W. (2006) Influenza report.

4. Clinical guidelines Influenza in adults. Non-profit corporate organization "International Association of Infection Professionals" ("ISSAI"). Ministry of Health of the Russian Federation, 2017.

5. https://www.who.int/ru/news-room/detail/14-12-2017-up-to-650-000-people-die-of-respiratory-diseases-linked-to-seasonal-flu- each-year

6. Jackson, ML., Chung, JR., Jackson, LA., Phillips, CH., Benoit, J., Monto, AS., et al. (2017) Influenza Vaccine Effectiveness in the United States during the 2015–2016 Season. N Engl J Med. 377(6): 534-543.

7. Cowling, BJ., Chan, KH., Fang, VJ., Cheng, CK., Fung, RO., Wai, W., (2009) Facemasks and hand hygiene to prevent influenza transmission in households: a cluster randomized trial. Ann Intern Med, 151(7): 437-446.

8. https://www.elibrary.ru/item.asp?id=39389452 (access 15/10/2021)