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Correction of the oropharyngeal and gut microbiota in children by plant extracts containing natural products

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ABSTRACT

The widespread use of antibacterial drugs for the treatment of respiratory diseases causes antimicrobial resistance in opportunistic microorganisms, which leads to the chronic forms of respiratory diseases and contributes to the risk of repeated respiratory infections. One of the new therapeutic solutions is the use of multicomponent water-soluble plant extracts. The goal of this study was to evaluate the antibacterial efficacy of the extracts of multicomponent herbal remedies versus the synthetic antiseptic for the treatment of the oropharyngeal and gut opportunistic microflora in children with chronic tonsillitis.

In a retrospective study, we compared the effectiveness of the plant extract Tonzinal (experimental group, 100 patients) versus the Miramistin antiseptic agent (control group, 40 patients) for the treatment of chronic tonsillitis in children 5 to 15 years old using various treatment regimens.

The oropharyngeal microbiocenosis was investigated by the bacteriological analysis of smears from the posterior wall of the pharynx and tonsils. Bacterial strains were isolated by inoculation on liquid agar media with the subsequent identification of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Candida* spp., *Moraxela cataralis*, and *Mycoplasma pneumonie* according to the morphological and biochemical characteristics. For the bacteriological analysis of gut microbiocenosis, *Staphylococcus aureus*, *Streptococcus* spp., *Candida* spp., *Klebsiella* spp., *Clostridiums* spp., and *Proteus* spp. were isolated from the fecal filtrate and then identified by the same methods. The occurrence rate of microorganisms in patients of the experimental and control groups was compared before and after the 10-day course of therapy.

A statistically significant decrease in the occurrence rate of *Staphylococcus aureus* (from 25% to 0%, $p<0.01$) and *Candida* spp. (from 18% to 0%, $p<0.01$) in the oropharynx of patients in the experimental group and from 20% to 7.5% and from 5% to 0% ($p<0.05$), respectively, in the control group was observed. A statistically significant decrease in the occurrence rate of *Streptococcus pyogenes* was only observed in the experimental group (from 30% to 0%, $p<0.01$). Treatment with Tonzinal or Miramistin did not lead to the statistically significant changes in the occurrence rate of opportunistic microorganisms in the gut microflora of the patients in both groups. Therefore, we have shown a higher antimicrobial efficacy of Tonzinal versus the Miramistin antiseptic for the treatment of the oropharyngeal opportunistic microorganisms in children with chronic tonsillitis.

Keywords: respiratory infections, antibiotic resistance, microbial migratory aggression, phytopreparations, Tonzinal, Miramistin

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INTRODUCTION

Respiratory infections remain an urgent medical and socio-economic problem in Russia. According to the Ministry of Health of the Russian Federation, the incidence of respiratory infections in 2017-2018 was 20,000-25,000 per a population of 100,000 [1]. Respiratory infections spread at a high rate and have an epidemic character. The SARS-CoV-2 pandemic, which we have been observing over the past two years, can serve as an example [1]. The irrational use of antibiotics for the treatment of respiratory diseases increases the group of patients susceptible to repeated respiratory infections due to emerging resistance to antibiotics (the risk group) [2, 3]. People who belong to the risk group suffer from inflammatory diseases of the oropharynx, such as tonsillitis, pharyngitis, gingivitis, periodontitis, etc. often and for a long period of time [4].

The use of antibiotics for the treatment of respiratory diseases has a negative impact not only on the microflora of the oropharynx, but also on the microflora of other biotopes – the intestines, urogenital tract, and skin [5]. Therefore, acute respiratory diseases turn into chronic forms with the possibility of the persistence of antibiotic-resistant microorganisms in other biotopes, which increases the incidence of acute diseases [6].

The analysis of the literature data [6, 7] as well as our own results show that the migration of antibiotic-resistant opportunistic microorganisms from one biotope to another – that should be referred to as microbial migratory aggression – leads to the spread of dysbiosis to different biotopes of the macroorganism. The migration of microorganisms between different loci was confirmed recently by molecular genetic methods [8, 9, 10]. Therefore, a change in the antibiotic resistance of microorganisms in one biotope leads to a disruption in the global balance between the microbiota and the macroorganism, weakens their symbiosis, and enhances the risk of mutual aggression between the macroorganism and its microbiota [11, 12].

The number of cells of human microbiota – all microorganisms that live on and inside the human body – is tenfold greater than the number of cells of the human body (macroorganism) itself. While the human genome contains about 22,000 genes, the human microbiome contains about 8 million unique genes, i.e. 360 times more than there are human genes [13]. Therefore, an imbalance of microorganisms with the possible dominance of opportunistic species with acquired resistance to antibiotics can significantly weaken the protective function of normal microflora by suppressing its colonization activity and increase the frequency of respiratory diseases [14]. In addition, dysbiotic changes affect the general well-being as well as the cognitive and physical development of a person [11].

It is known that natural phytopreparations, based on water-soluble extracts of medicinal herbs produced using an innovative extraction method, have a milder effect on the microflora than synthetic antiseptics, and at the same time efficiently reduce bacterial colonization by opportunistic microorganisms. In addition, the use of phytopreparations is considered more benign for the indigenous microflora. However, at the same time, they are quite effective in reducing microbial contamination by opportunistic microorganisms. Concentrated extracts of calendula, yarrow, St. John’s wort, and licorice are widely used in herbal medicines [15].

Therefore, the study of the suppression rate of bacterial colonization by opportunistic microflora of the oropharynx and intestines in patients with acute respiratory diseases by the extracts of calendula, yarrow, St. John’s wort, and licorice that are the components of the natural remedy Tonzinal, versus the antiseptic Miramistin is of significant interest.

The goal of this study was to compare the effectiveness of the antimicrobial action of the multicomponent herbal preparations versus a synthetic antiseptic on the oropharynx and intestine opportunistic microflora in 5 to 15 year old children with a chronic tonsillitis diagnosis.

MATERIALS AND METHODS

In this retrospective study, we compared the efficacy of two treatment regimens for chronic tonsillitis in 5 to 15 year old children.

One hundred and forty children who were 5 to 15 years old (mean age is 10±2.5 years) and had a confirmed diagnosis of chronic tonsillitis participated in this study. The major group – 130 children (93%) – were school-age children and the rest – 10 children (7%) – were preschoolers. The experimental and control groups had a homogeneous age distribution. The patients were seen by the doctor at the time of the exacerbation of chronic tonsillitis on the 1st-3rd day of illness; 85% of the patients had a history of more than 5 episodes of acute respiratory infections and were at risk of repeated respiratory infections. The patients received symptomatic treatment. The gender differences were not taken into consideration. The exclusion criteria included individual intolerance to the drug, complications with subsequent transfer of the patient to a hospital, and refusal of the patient to participate in the study.

The chronic tonsillitis was diagnosed by an otolaryngologist based on clinical and anamnestic data, physical diagnosis, and laboratory data. The patients were treated on an outpatient basis and were divided into

2 groups – experimental group and control group – depending on the treatment regimen. The patients of the experimental group (100 children) and the control group (40 children) with a diagnosis of chronic tonsillitis underwent a 10-day course of treatment. The treatment was carried out by washing the lacunae of the tonsils with a solution of the phytopreparation Tonzinal (Saluta-M, Russia) for the patients in the experimental group and with the antiseptic agent Miramistin (0.01% aqueous solution of benzyldimethyl [3–(myristoylamino)propyl] ammonium chloride monohydrate, Infamed, Russia) for the patients of the control group 3-4 times a day during the entire period of therapy. This treatment was combined with a standard ultrasonic stable impact on the projection area of the palatine tonsils for 3-4 min with an intensity of 0.05 W/cm^2 using the UZT-101 physiotherapy apparatus.

The state of microbiocenosis of the oropharynx and intestines were followed according to the bacteriological data on the occurrence rate of opportunistic microflora in smears from the posterior pharyngeal wall and tonsils as well as the content of opportunistic microorganisms in the fecal filtrate. After the course of treatment with the corresponding medicine, a repeated bacteriological examination was performed. All of the patients were examined on an outpatient basis.

Samples for analysis (smears from the posterior pharyngeal wall and tonsils, the fecal filtrate) were collected on the 1st and 10th days of treatment and delivered to the laboratory within three hours at the corresponding temperature. Bacteriological analysis of the fecal filtrate was performed by the tenfold serial dilution method followed by inoculation on selective liquid agar media. Smears from the posterior pharyngeal wall were seeded on liquid agar media in sectors. The identification of the isolated strains was performed based on morphological properties and using biochemical reactions. The number of bacteria was calculated by the number of a colony-forming unit (CFU) per gram of sample [16]. To determine the occurrence rate of opportunistic microflora at a concentration of more than 10^4 CFU/g, we analyzed the number of colonies of identified microorganisms before the start of treatment and after a 10-day course of therapy. Statistical data processing was carried out using descriptive statistics methods. The assessment of the statistically significant differences between the groups was performed according to the Pearson's goodness-of-fit test (χ^2) at a significance level of $p<0.05$ [17].

RESULTS

The results of the bacteriological analysis of the microflora of the intestines of patients in the experimental and control groups on the 1st and 10th days of treatment are presented in Tables 1 and 2.

From the data presented in Table 1, it follows that at least 30% of the patients in the experimental group and 20% of the patients in the control group had a high intensity of bacterial colonization of the tonsils before treatment, which corresponds to the dysbiotic state of oropharyngeal microbiocenosis that requires correction. There were no statistically significant differences between the experimental group and the control group in the occurrence rate of the studied microorganisms on the posterior pharyngeal wall and tonsils. Treatment with phytopreparation Tonzinal and the antiseptic agent Miramistin led to a decrease in the intensity of the bacterial colonization of the posterior pharyngeal wall and tonsils in patients.

As a result of the treatment, the occurrence rate of *Staphylococcus aureus* and *Candida* spp. decreased significantly: in the experimental group from 25% to 0% and from 18% to 0%, respectively ($p<0.01$), and in the control group from 20% to 7.5% and from 5% to 0%, respectively ($p<0.05$). The occurrence rate of *Streptococcus pyogenes* only showed a statistically significant decrease in the

Table 1. The intensity of the bacterial colonization of the posterior pharyngeal wall and tonsils in patients with chronic tonsillitis before and after the treatment

Microorganisms	Experimental group (n=100)			Control group (n=40)		
	The number of patients (occurrence rate, %)		Statistical significance, p	The number of patients (occurrence rate, %)		Statistical significance, p
	Day 1	Day 10		Day 1	Day 10	
Staphylococcus aureus	25 (25%)	0 (0%)	<0.01**	8 (20%)	3 (7.5%)	0.017*
Streptococcus pyogenes	30 (30%)	0 (0%)	<0.01**	2 (5%)	1 (2.5%)	0.361
Candida spp.	18 (18%)	0 (0%)	<0.01**	2 (5%)	0 (0%)	0.0253*
Moraxela cataralis	8 (8%)	2 (2%)	0.057	3 (7.5%)	1 (2.5%)	0.114
Mycoplasma pneumonie	5 (5%)	1 (1%)	0.102	–	–	–

The statistically significant differences of the corresponding values obtained on the 1st and 10th days of treatment were calculated according to Pearson's goodness-of-fit test, (*) indicates p<0.05, (**) indicates p<0.01.

Table 2. The intensity of the colonization of the intestine by opportunistic bacteria in patients before and after the treatment

Microorganisms	Experimental group (n=100)			Control group (n=40)		
	The number of patients (occurrence rate, %)		Statistical significance, p	The number of patients (occurrence rate, %)		Statistical significance, p
	Stage 1	Stage 2		Stage 1	Stage 2	
Staphylococcus aureus	12 (12%)	8 (8%)	0.37	5 (12.5%)	5 (12.5%)	1.0
Streptococcus spp.	9 (9%)	6 (6%)	0.43	3 (7.5%)	2 (5%)	0.48
Candida spp.	11 (11%)	8 (8%)	0.49	4 (10%)	3 (7.5%)	0.55
Klebsiella spp.	3 (3%)	1 (1%)	0.31	2 (5%)	2 (5%)	1.0
Clostridiums spp.	3 (3%)	2 (2%)	0.65	1 (2.5%)	1 (2.5%)	1.0
Proteus spp.	1 (1%)	1 (1%)	1.0	1 (2.5%)	1 (2.5%)	1.0

experimental group (from 30% to 0%, p<0.01), which indicates a higher antimicrobial efficacy of Tonzinal compared to Miramistin against opportunistic oropharyngeal microorganisms. There is a trend toward a decrease in the occurrence rate of *Streptococcus pyogenes* in the control group. The occurrence rate of *Moraxella catarrhalis* tends to decrease in both groups. Therefore, when analyzing the microflora of the palatine tonsils, the antimicrobial effect was more pronounced in the experimental group patients treated with Tonzinal compared to the patients in the control group. The intensities of bacterial colonization of the intestinal microbiocenosis in both experimental and control groups of patients before (stage 1) and after (stage 2) the treatment are presented in Table 2.

As it follows from the data shown in Table 2, at least 12% of patients in the experimental group and at least 12.5% of patients in the control group had intestinal microflora dysbiosis, which requires correction, due to the bacterial colonization of the fecal filtrate by opportunistic microorganisms. Both the experimental group and the control group were homogeneous. No statistically significant changes in the occurrence rate of opportunistic microorganisms were found in the intestinal microflora of the patients in the experimental and control groups after the medical treatment. The observed trends toward a more significant decrease in the occurrence rate of *Staphylococcus aureus*, *Candida* spp., *Klebsiella* spp., and *Clostridiums* spp. in the experimental group versus the control group may indicate a higher efficiency of Tonzinal, which requires a further experimental confirmation.

DISCUSSION

Analysis of the statistically significant data obtained in this study allows us to conclude that the occurrence rate of the opportunistic microflora in the oropharynx is more efficiently reduced by the treatment with phytopreparation Tonzinal than with the antiseptic Miramistin. Treatment with phytopreparation Tonzinal did not lead to statistically significant changes in the intestinal microbiocenosis, although a trend toward a decrease in the occurrence rate of most opportunistic microorganisms was observed. Since an integral assessment of microbiocenoses was not the goal of this study, only the occurrence rate of opportunistic microflora was assessed when comparing treatment with two medical preparations while the assessment of the state of microbiocenoses of the oropharynx and intestines was not performed. As it was shown in publications describing the effect of antiseptics and herbal remedies on the state of microbiocenoses of the oropharynx and intestines, herbal remedies have a milder effect on the indigenous microflora of these organs than antiseptics [18, 19, 20].

It is known that many types of intestinal microorganisms are of oral origin. That indicates the possibility of the translocation of microorganisms involved in the antibiotic resistance genes transfer as well as those responsible for anti-lysozyme, anti-interferon, and anti-cytokine activity from the oropharynx to the intestine [21]. The horizontal gene transfer by the temperate bacteriophages, which are more mobile and more resistant to aggressive environments with significantly lower and/or higher pH than microorganisms, plays an important role in the transmission of the above-mentioned dysbiosis factors including the transfer of antibiotic resistance genes [14]. Therefore, the suppression of opportunistic microflora in the oral cavity can affect the number of opportunistic strains in the intestine, shifting the balance in favor of the indigenous microflora.

In order to reduce global antimicrobial resistance and prevent the formation of superbugs – microorganisms that are resistant to all known antimicrobial drugs – a decision was made to use alternative methods for combating pathogenic and opportunistic microorganisms within the framework of the Eurasian Economic Union. The modern methods of highly specific targeting and elimination of bacteria include the use of virulent bacteriophages, bacteriocins, and phytopreparations with the maximum concentration of useful compounds in the form of lyophilized plant extracts [22]. The latter are more naturally involved in the biochemical processes of the human body, do not cause toxic reactions, and are notable for their sparing effect. Due to the complexity of the chemical composition inherent for the plants' natural compounds, phytopreparations have a variety of biological effects interacting with several receptors and affecting pathogenetic factors simultaneously. In addition to a positive effect on microbiocenoses, phytopreparations suppress the development of functional disorders in internal organs and stimulate metabolism [19].

It has been shown that the greatest positive effect of herbal remedies on local and general immunity, the state of microflora, and metabolism is manifested in the course of their long-term use that determines the specificity and value of these medical preparations [10]. The therapeutic and healing effect of herbal products is durable and long lasting. The effectiveness of phytopreparations is determined by their content, namely by biologically active compounds such as alkaloids, flavonoids, essential oils, vitamins, polysaccharides, and amino acids. Different plant species as well as different parts of the plants contain these compounds in variable concentrations [23]. The above-mentioned properties allow us to consider the possibility of a wider application of harmless and highly effective herbal remedies as antimicrobial drugs.

The herbal preparation Tonzinal showed good efficacy in the treatment of tonsillitis. The results of our study showed that its activity in the treatment of tonsillitis significantly exceeds the activity of the synthetic antiseptic Miramistin.

CONCLUSION

The occurrence rate of opportunistic microflora in the oropharynx and intestines of patients with chronic tonsillitis is effectively reduced by treatment with both multicomponent natural remedies based on herbal extracts and synthetic antimicrobial drugs. The effectiveness of multicomponent natural remedies can be higher than that of antimicrobial drugs due to the lack of resistance of opportunistic microorganisms to herbal remedies.

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