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THE USE OF MIRAMISTIN IN THE TREATMENT OF CHRONIC GINGIVITIS IN CHILDREN WITH CYSTIC FIBROSIS

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Abstract

The study involved an assessment of the time course of hygienic, periodontal indices and criteria of local immunity of the oral cavity in children with cystic fibrosis, secondary to prescribed therapy. Study participants diagnosed with chronic catarrhal gingivitis were prescribed antiseptic Miramistin as part of standard treatment. The study implied a comparison of the results of the measures taken in relation to the initial condition of patients and conclusions about the effectiveness of Miramistin in the treatment of gingivitis.

The use of the antiseptic Miramistin in the complex treatment of chronic gingivitis has had a positive effect on the clinical time course of gingivitis. Statistically significant improvement of the studied indicators in comparison with their initial values during the observation period was determined. The treatment had a positive effect on such etiological factors of gingivitis in children with cystic fibrosis, as the level of oral hygiene, microbial contamination and protective properties of oral fluid.

Keywords: *antiseptic, chronic catarrhal gingivitis, cystic fibrosis, children*

Introduction

The high level of periodontal disease in children is one of the current medical problems [1-3]. The combined influence of general and local factors, namely environmental conditions, specific reactions of the body, bacterial pathogens and the state of immunity determines the development of inflammatory process in the periodontium [4, 5].

Numerous scientific studies have been devoted to the study of pathogenic interdependence between somatic disease and lesions of the oral cavity [4, 6]. A significant prevalence of inflammatory gum disease in children with endocrine, gastroenterological disorders, vegetative-vascular disorders and so forth has been established [7, 8]. Scientific research in recent years has focused mainly on determining the mechanisms of the relationship between somatic and dental diseases, which mutually aggravate the course of the disease [9, 10].

The study of rare diseases is among the priority areas in medicine today [11, 12]. Every year the number of such diseases grows. Cystic fibrosis, a hereditary autosomal recessive disease characterized by multiorgan disorders, severe course and complex prognosis, is one of the most common among them [13, 14].

Today, cystic fibrosis is known to be associated with the development of lesions of the oral cavity in children [15, 16]. At an early age, patients with cystic fibrosis show signs of gingivitis. The high prevalence and early manifestation of the disorder is due to both the general impact of somatic disease and local factors, such as activation of pathogenic microflora [17], low level of hygiene and sanitation of the oral cavity, changes in rheological and protective properties of oral fluid [18].

The microbiota of dental plaque, which realizes its pathogenic potential against the background of reduced protective factors of the body, is considered the main etiological factor of dental diseases. Cystic fibrosis is characterized by chronic colonization of the respiratory tract by pathogenic microflora, which transits into the oral cavity, changes microbial spectrum and also affects the course of inflammatory diseases of periodontal tissues [14, 15].

It is known that in the early stages of gingivitis inflammatory signs are reversible. And to prevent the development of more severe forms of lesions, it is necessary to implement a set of treatment and prevention measures aimed at hygienic care of the oral cavity and the use of topical agents with antibacterial activity stimulating the protective mechanisms of the oral cavity [10].

"Soft" antiseptic agents are most commonly used to reduce the pathogenicity of the oral microflora in pediatric dental practice. Miramistin, an agent from the pharmacotherapeutic group of antiseptics and disinfectants, is one of the effective broad-spectrum antiseptics [19, 20].

Miramistin activity extends to a wide range of bacteria, including strains resistant to antibiotics. Also, the agent has an antifungal effect, stimulates the activity of immunocompetent cells. It is used in the form of irrigation, applications, electrophoresis. An important property of Miramistin is its ability to enhance the anti-inflammatory, trophic, immunomodulatory effect of galvanic current during physiotherapy [19, 20]. At the same time, this antiseptic retains its healing properties. In view of the above, it is advisable to use Miramistin in the complex treatment of gingivitis in children with cystic fibrosis. So, the purpose of our study was evaluation of clinical effectiveness of the antiseptic Miramistin in the complex treatment of chronic gingivitis in children with cystic fibrosis.

Methods

The study involved 30 children aged 3 to 17 years with a confirmed diagnosis of cystic fibrosis (main group). All children were diagnosed with chronic generalized catarrhal gingivitis. The control group included 23 children of similar age, somatically healthy. The study implied comparison of the results of treatment in the main group in relation to the initial condition of patients.

Clinical examination of patients included determination of the Fedorov-Volodkina hygiene index (HI), gingivitis index (PMA) [9], sampling of unstimulated oral fluid.

The state of local immunity was assessed by determination of the level of secretory immunoglobulin sIgA, lysozyme activity and urease

in the oral fluid. Enzyme-linked immunosorbent assay was used to study sIgA. Lysozyme activity was evaluated by bacteriolytic method using a suspension of *Micrococcus lysodeickicus* as a substrate and urease activity in oral fluid was determined using Nessler's reagent and urea solution. The degree of oral lysozyme and urease ratio was used to calculate the degree of oral dysbiosis.

During the study, all patients were instructed in the rules of oral hygiene and followed the prescriptions of the gingivitis treatment protocol. Antiseptic treatment of gums involved administration of 0.01% solution of Miramistin in the form of oral baths. Miramistin electrophoresis on the area of the parotid salivary glands was also prescribed once a day. Treatment was carried out for 10 days.

The findings were statistically processed using Microsoft Excel and Statistica 8.0 application packages for statistical data analysis with the calculation of the arithmetic mean (M) and the mean errors (m). The probability of the obtained results was evaluated by the criterion of Student's reliability. Differences in the comparative groups were considered significant at $p < 0.05$.

Results

Analyzing the results of the study, we found that prior to treatment, hygiene index in the main group was, on average, 2.39±0.17, which corresponds to "unsatisfactory" hygiene. No child had a "good" level of oral hygiene. The PMA index reflects the degree of severity of gingivitis. Evaluation of the index revealed significant differences in the main and control groups, namely 47.98±3.47 and 9.17±2.29, respectively. The average value of the index in the main group corresponds to the moderate severity of gingivitis (Table 1).

Immunological parameters in the group of children with cystic fibrosis were found to have the following values: sIgA – 92.62±2.44 ml/l, lysozyme activity – 10.29±0.27 RU/l, urease activity – 9.56±0.37 µmol/min/l. The degree of dysbiosis of the oral cavity before treatment was 3.25 units. Indicators of the studied parameters in the control group differed significantly (Table 2).

After the treatment, the obtained data of the studied parameters show a significant improvement in the hygienic and periodontal condition and the level of local immunity (Table 3).

Discussion

Poor oral hygiene is accompanied by an increase in the volume of plaque, resulting in species replacement of microorganisms and the emergence of anaerobic species with pronounced pathogenic properties [9]. These microorganisms produce endotoxins and enzymes that directly damage periodontal tissue cells and contribute to the weakening of protective mechanisms [8, 9].

Pathogenic mechanisms of cystic fibrosis trigger a decrease in the level of salivation, an increase in the viscosity of the oral fluid, and a suppression of the local immunity. The content of immunoglobulins and proteins involved in antimicrobial protection is disturbed by insufficient saliva secretion [16]. These criteria in the complex can be considered as factors in the development of gingivitis in children with cystic fibrosis. When determining treatment and prevention measures, it is important to identify the possibility of influencing these factors.

The results of the study indicate that patients with cystic fibrosis have significant interdependent changes in all links of the local immunity. The values of all studied indicators had significant differences in both groups. There was a 1.4-fold decrease in the concentration of sIgA in children of the main group compared with the control group. The decrease in the level of sIg A can be explained by a reduced secretory activity of the salivary glands in cystic fibrosis and the active action of microbial hydrolases, which are able to cleave the dimeric form of IgA [21, 22]. In addition, children in the main group showed an almost 1.5-fold statistically significant decrease in lysozyme activity and a 2.2-fold increase in urease activity, which indicates an increase in the activity of microorganisms that produce it.

Disturbances in the local immune system may [23] be accompanied by further exacerbation of infectious diseases of the oral cavity in patients with cystic fibrosis. This systemic disease triggers changes in the immunobiological reactivity of the body, reducing the protective reactions that provide

resistance to the tissues of the oral cavity and surrounding tissue [24, 25].

Our study showed an improvement compared to baseline. All the patients were found to have an improvement in the clinical condition of the gums. Satisfactory hygienic condition of the oral cavity and reduction of periodontal index values were revealed. A 1.6-fold decrease in the degree of oral dysbiosis indicates a significant reduction in the imbalance among the microbiota of plaque. The strengthening of the level of local immunity is evidenced by a significant increase in sIgA and lysozyme activity (1.2 times, $p < 0.01$) in oral fluid.

In general, it can be stated about the need for more in-depth studies on both the etiology and comorbidity of these conditions with the study of familial [16], epidemiological [26], geographical data using modern research methods [27, 28]. The studies carried out will make it possible to determine the actual connection between cystic fibrosis and oral pathology [29, 30] in pediatric practices.

We conclude that the use of the antiseptic Miramistin in the complex treatment of chronic gingivitis has had a positive effect on the clinical time course of gingivitis. Statistically significant improvement of the studied indicators in comparison with their initial values during the observation period was determined. The treatment had a positive effect on such etiological factors of gingivitis in children with cystic fibrosis, as the level of oral hygiene, microbial contamination and protective properties of oral fluid.

During treatment with Miramistin, no signs of side effects were found on the oral mucosa or on the skin of patients. The children tolerated the prescribed procedures well and did not notice any discomfort. Thus, the positive effect in the clinical and immunological status in patients with gingivitis allows to recommend Miramistin in the complex of traditional treatment of the disease.

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References

1. Carrard VC, van der Waal I. The role of the dentist in the diagnosis and management of patients with oral mucosal diseases. *Med Oral Patol Oral Cir Bucal*. 2021;26(2):e256-e260. Published 2021 Mar 1. doi:10.4317/medoral.24465
2. Nazaryan R, Kryvenko L. Salivary oxidative analysis and periodontal status in children with atopy. *Interv Med Appl Sci*. 2017;9(4):199-203. doi:10.1556/1646.9.2017.32
3. Polyvianna Y., Chumachenko D., Chumachenko T. Computer aided system of time series analysis methods for forecasting the epidemics outbreaks. 2019 15th International Conference on the Experience of Designing and Application of CAD Systems, CADSM 2019:1-4. doi: 10.1109/CADSM.2019.8779344
4. Denga O, Pyndus T, Gargin V, Schneider S. Influence of metabolic syndrome on condition of microcirculatory bed of oral cavity. *Georgian Med News*. 2017;(273):99-104.
5. Nazaryan RS, Kryvenko LS, Gargin VV. The role of nitric oxide synthase in the modulation of the immune response in atopic disease. New Armenian Med J 2017;11(2):52-57.
6. Fesenko D, Glazunov O, Nakonechna O, Nazaryan R, Gargin V. Consequences of microsequences of microcirculatory distrurbances of oral mucosa in modeling of rheumatoid arthritis. *Georgian Med News*. 2019;(295):137-140.
7. Pathak JL, Yan Y, Zhang Q, Wang L, Ge L. The role of oral microbiome in respiratory health and diseases. *Respir Med*. 2021;185:106475. doi:10.1016/j.rmed.2021.106475
8. Popova TM, Kryvenko LS, Tishchenko OV, Nakonechna OA, Podrigalo LV, Nessonova TD, et al. Effect of Electronic Cigarettes on Oral Microbial Flora. J Pharm Nutr Sci 2021;11(1):54-64.
9. Nazaryan R, Kryvenko L, Zakut Y, Kamaukh O, Gargin V. Application of estimated oral health indices in adolescents with tobacco

addiction. *Pol Merkur Lekarski*. 2020;48(287):327-330.

10. Kovach I, Kravchenko L, Khotimska Y, Nazaryan R, Gargin V. Influence of ozone therapy on oral tissue in modeling of chronic recurrent aphthous stomatitis. *Georgian Med News*. 2017;(264):115-119.
11. Molina-García A, Castellanos-Cosano L, Machuca-Portillo G, Posada-de la Paz M. Impact of rare diseases in oral health. *Med Oral Patol Oral Cir Bucal*. 2016;21(5):e587-e594. Published 2016 Sep 1. doi:10.4317/medoral.20972
12. Graves DT, Corrêa JD, Silva TA. The Oral Microbiota Is Modified by Systemic Diseases. *J Dent Res*. 2019;98(2):148-156. doi:10.1177/0022034518805739
13. Herman K, Kowalczyk-Zając M, Pytrus T. Oral cavity health among cystic fibrosis patients: Literature overview. *Adv Clin Exp Med*. 2017;26(7):1147-1153. doi:10.17219/acem/64054
14. Pawlaczyk-Kamieńska T, Borysewicz-Lewicka M, Śniatała R, Batura-Gabryel H, Cofta S. Dental and periodontal manifestations in patients with cystic fibrosis - A systematic review. *J Cyst Fibros*. 2019;18(6):762-771. doi:10.1016/j.jcf.2018.11.007
15. Duruel O, Berker E, Özşin-Özler C, et al. Levels of pro- and anti-inflammatory cytokines in cystic fibrosis patients with or without gingivitis. *Cytokine*. 2020;127:154987. doi:10.1016/j.cyto.2020.154987
16. Nazaryan R, Tkachenko M, Kovalenko N, Babai O, Kamaukh O, Gargin V. Analysis of local immunity indicators of the oral cavity and degree of gingivitis depending on mutation of CFTR gene in children with cystic fibrosis. *Georgian Med News*. 2019;(296):27-31.
17. Vieira Colombo AP, Magalhães CB, Hartenbach FA, Martins do Souto R, Maciel da Silva-Boghossian C. Periodontal-disease-associated biofilm: A reservoir for pathogens of medical importance. *Microb Pathog*. 2016;94:27-34. doi:10.1016/j.micpath.2015.09.009
18. Lynge Pedersen AM, Belstrøm D. The role of natural salivary defences in maintaining a healthy oral microbiota. *J Dent*. 2019;80 Suppl 1:S3-S12. doi:10.1016/j.jdent.2018.08.010
19. Osmanov A, Farooq Z, Richardson MD, Denning DW. The antiseptic Miramistin: a review of its comparative in vitro and clinical activity. *FEMS Microbiol Rev*. 2020;44(4):399-417. doi:10.1093/femsre/fuaa012
20. Danilova TA, Danilina GA, Adzhieva AA, et al. Effects of Miramistin and Phosprenil on Microbial Biofilms. *Bull Exp Biol Med*. 2017;163(4):439-442. doi:10.1007/s10517-017-3823-x
21. Joo NS, Cho HJ, Shinbashi M, et al. Combined agonists act synergistically to increase mucociliary clearance in a cystic fibrosis airway model. *Sci Rep*. 2021;11(1):18828. Published 2021 Sep 22. doi:10.1038/s41598-021-98122-5
22. Abu-Zahra R, Antos NJ, Kump T, Angelopoulou MV. Oral health of cystic fibrosis patients at a north american center: A pilot study. *Med Oral Patol Oral Cir Bucal*. 2019;24(3):e379-e384. Published 2019 May 1. doi:10.4317/medoral.22756
23. Bondarenko AV, Pokhil SI, Lytvynenko MV, Bocharova TV, Gargin VV. Anaplasmosis: experimental immunodeficient state model. *Wiad Lek*. 2019;72(9 cz 2):1761-1764.
24. Nechyporenko AS, Alekseeva VV, Sychova LV, Cheverda VM, Yurevych NO, Gargin VV. Anatomical prerequisites for the development of rhinosinusitis. Lek Obz 2020;6(10):334-338.
25. Narang A, Maguire A, Nunn JH, Bush A. Oral health and related factors in cystic fibrosis and other chronic respiratory disorders. *Arch Dis Child*. 2003;88(8):702-707. doi:10.1136/adc.88.8.702
26. Chumachenko D., Chumachenko T. Intelligent Agent-Based Simulation of HIV Epidemic Process. Adv Intell Sys Comput 2020;1020:175-188. doi: 10.1007/978-3-030-26474-1_13
27. Krivenko S, Lukin V, Krylova O, Kryvenko L, Egiazarian K. A fast method of visually lossless

compression of dental images. Appl Sci 2021;11(1):1-14.

28. Gargin V., Radutny R., Titova G., Bibik D., Kirichenko A., Bazhenov O. Application of the computer vision system for evaluation of pathomorphological images. 2020 IEEE 40th International Conference on Electronics and Nanotechnology, ELNANO 2020 - Proceedings; 2020. 469-473, doi: 10.1109/ELNANO50318.2020.9088898.
29. Ajonuma LC, He Q, Sheung Chan PK, et al. Involvement of cystic fibrosis transmembrane conductance regulator in infection-induced edema. *Cell Biol Int*. 2008;32(7):801-806. doi:10.1016/j.cellbi.2008.03.010
30. Guimarães JR, Carvalho LG, Damascena LC, et al. The incidence of severe oral mucositis and its occurrence sites in pediatric oncologic patients. *Med Oral Patol Oral Cir Bucal*. 2021;26(3):e299-e303. Published 2021 May 1. doi:10.4317/medoral.24185

Table 1. Indicators of oral hygiene and periodontal status in the examined children

Indicator	Total, (M±m)	
	Main group, n = 30	Control group, n = 23
HI	2.39±0.17*	1.61±0.11
PMA	47.98± 3.47*	9.17±2.29

Note. * statistically significant difference (p <0.01) between comparison groups

Table 2. Indicators of factors of local immunity of the oral cavity in oral fluid in the examined children, mg/l

Indicator	Total, (M±m)	
	Main group, n = 30	Control group, n = 23
sIgA , mg/l	92.62±2.44*	132.5±7.67
Lysozyme activity, RU/l	10.29±0.28**	15.37±0.29
Urease activity, µmol/min/l	9.56±0.37**	4.37±0.15
Dysbiosis degree	3.25	1.00

Note. * probability of change (p <0.01) compared to the control

** probability of change (p <0.05) compared to control

Table 3. Time course of indicators of the studied parameters after the treatment, (M ± m)

Indicators	Before treatment	After treatment
HI	2.39±0.17	1.70±0.05*
PMA	47.98± 3.47	36.95±2.49**
sIgA , mg/l	92.62±2.44	106.60±2.19*
Lysozyme activity, RU/l	10.29 ± 0.27	12.41±0.13*
Urease activity, µmol/min/l	9.56±0.37	6.94±0.15
Dysbiosis degree, units	3.25	1.96