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IMPROVING THE EFFECTIVENESS OF THE TREATMENT OF XEROSTOMIA IN PATIENTS CONFRONTED COVID-19

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Abstract

COVID-19 caused by an emerging pathogen SARS-CoV-2 is able to lead to various pathological conditions in the oral cavity. Of huge importance is the risk of xerostomia which can occur in both during the height of the disease and after recovery from this novel coronavirus infection. A possible risk factor for xerostomia in patients with COVID-19 may be the impact of SARS-CoV-2 on the expression of angiotensin-converting enzyme 2 by salivary gland cells. Efforts are under way in many countries to treat and minimize the so called post-COVID syndrome. Our clinical and epidemiological study was aimed at studying the effectiveness of the treatment of xerostomia in patients with COVID-19. The research question required an observational, prospective, sampling, controlled open before-after intervention study design. This paper describes the potential of using modern moisturizing polycomponent toothpastes in patients with signs of xerostomia who have undergone COVID-19.

The study included 40 patients of both sexes, aged 32 to 44 years. 78±6.6% were female participants. Research methods such as medical and dental examination, sialometry test for measuring saliva flow, as well as statistical analysis and interpretation were used.

Our research has shown that the application of moisturizing toothpaste can improve salivation and subjective sensations of this group of patients. In addition, we have outlined approaches to the construction of further clinical and epidemiological studies of effectiveness of interventions similar in nature. In turn, this will allow us to make more accurate and maximally unbiased judgments about prophylactic and therapeutic effects of such interventions.

Keywords: COVID-19, complication, xerostomia, oral cavity, toothpaste.

Introduction

The emerging coronavirus infection (COVID-19) pandemic continues to be the focus of scientific attention around the world [*WHO, 2021*]. On our planet the number of people infected with COVID-19 in April 2021 exceeded 137 million people, while 2.2% of the disease resulted in death [*John Hopkins COVID map, 2021*]. At present, colossal efforts are being made to contain the epidemic spread of SARS-CoV-2. Nevertheless, COVID-dissidence, infodemia, the often emerging rejection of anti-epidemic measures in some countries, as well as the extreme politicization of vaccination campaigns, do not lose their relevance. Cases of this infection are being reported in all regions of the world, its spread is characterized by a significant medical and social burden, which is largely due to the high frequency of complications from various organs and systems of the human body. It is no coincidence that one can hear more and more often about the post-COVID syndrome and how to deal with it [*Nalbandian A, 2021*]. The significance and etiopathogenetic role of COVID-19 in persons with oral cavity diseases is of scientific interest.

The literature describes the following manifestations of COVID-19 in the oral cavity: halitosis, candidiasis, chronic recurrent herpes, chronic recurrent aphthous stomatitis, enanthema in the area

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of the hard palate. This list can be supplemented by xerostomia, which can occur both in the midst of an illness and after a coronavirus infection [*Makedonova Ju et al., 2021; Sugihartono T, 2020; Satygo E, Bakulin I, 2021*]. Xerostomia in patients with COVID-19 was firstly mentioned in [*Chen L et al, 2020*]. In a number of studies, the authors point to the manifestation of xerostomia as a harbinger of clinical symptoms of the disease, as well as one of the complaints of patients after suffering COVID-19 [*Sinjari B et al., 2020; Saniasiaya J, 2021; Farshidfar N, Hamedani S, 2021*].

According to [*Fantozzi P et al., 2020*], xerostomia turned out to be one of the most common symptoms (45.9%) in patients with COVID-19, outstripping olfactory dysfunctions in frequency (41.4%) and somewhat yielding to taste dysfunctions (59.5%). Of note, every third patient presented a combination of xerostomia with other manifestations. Another study suggested more than half (56%) of female patients could report xerostomia [*Biadsee A et al., 2020*]. Hyposalivation was observed in 18% of the examined patients. This study did not reveal significant differences in salivation between men (1.14±0.65) and women (1.12±0.43; p=0.928) [*Omezli M, Torul D, 2021*].

Xerostomia is known to develop secondary to a violation of the sense of smell, and this condition is the result of mouth breathing. However, no significant correlation was found between xerostomia and nasal congestion in patients with COVID-19 [*Biadsee A et al., 2020*].

A possible cause/risk factor for xerostomia in patients with COVID-19 may be the impact of SARS-CoV-2 on the expression of angiotensin-converting enzyme 2 by salivary gland cells. In turn, this reduces their secretory function [*Xu H et al, 2020*], promotes the development of inflammation of the salivary glands [*Wang C et al,. 2020*], and zinc deficiency [*Jothimani D et al., 2020; Vogel-González M et al., 2021*]. Moreover, a number of authors point to the neuroinvasive and neurotropic potential of the beta-coronavirus SARS-CoV-2 [*Freni F et al., 2020; Belchior Fontenele M, Pedrosa M, 2021*].

In light of the above data and the persisting epidemiological risks associated with the ongoing spread of COVID-19, it is relevant to search for treatments with proven efficacy and safety that are able to eliminate the symptoms of xerostomia. In addition, this has a significant contribution to improving the quality of life of patients with a history of previous COVID-19.The objective of this study was to improve the effectiveness of the treatment of xerostomia in patients who have undergone COVID-19.

Material and methods

We conducted an observational, prospective, sampling, controlled open before-after intervention study. The work was based on follow-up of 40 patients of both sexes aged 32 to 44 years (the mean age 37.6±10.2), after recovery from COVID-19. All persons underwent treatment and were under dispensary check-up at the dental clinic of Privolzhsky Research Medical University (Nizhny Novgorod). Among the participants, there were more female patients (78±6.6%). All participants were residents of the city of Nizhny Novgorod.

Patients of both sexes, with complaints of dry mouth, a history of confirmed COVID-19 were eligible for this study. Non-inclusion criteria included concomitant diseases of the oral mucosa, with prescription of antihypertensive drugs or antidepressants. Exclusion criteria were a patient's refusal from treatment and participation in the study, low compliance. The patients (n=40) were divided into two groups (I and II groups) of 20 people, comparable in age, sex, ethnicity, severity of manifestations of xerostomia. Moreover, the study design included a control group which consisted of 20 people aged 35±3.7 years without clinical signs of dry mouth.

In I group we administered a bundle of hygienic measures which included a moisturizing toothpaste containing sodium salt of pyrrolidone-carbolic acid, betaine, mallow extract and xylitol (President PROFI AQUA Xerostomed® manufactured by Zelenaya Dubrava, Russia). In II group, toothpaste with a fluorine

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

content of 1350 *ppm* was used for oral hygiene. The multiplicity and mode of using toothpastes in both groups were identical, i.e. twice a day, in the morning and in the evening. The course of intervention lasted 30 days. All participants completed follow-up.

The patients underwent sialometry according to the procedure of Pozharitskaya (1994): in the morning from 8 till 10 am, without prior food intake and brushing the teeth, saliva was collected by spitting into a graduated test tube with a division value of 0.1 *ml* for 10 minutes. After collecting saliva three times, an averaged value of an individual level of salivation of each patient was calculated, and then we determined a degree of xerostomia [*Makeeva I et al., 2013*].

Statistical analysis: With respect to the distribution normality (Shapiro-Wilk test, QQ-plots, fig. 1), continuous outcomes were accompanied by either mean (standard deviation) or median (interquartile range). We used the Pearson χ^2 test or Fisher's exact test for the analysis of categorical outcomes. We used either the ANOVA method or Kruskall-Wallis tests to compare the volume of saliva. Paired samples were handled with Wilcoxon test. When the comparison among all groups showed a significant difference, we did pairwise comparisons with Mann-Whitney test. Correlation analysis implied either Spearman (ρ) or Pearson (r) correlation. Hypothesis testing was two-sided and we considered p values of less than 0.05 to be significant. IBM SPSS 24 and R (v 4.0.2; R Foundation for Statistical Computing, Vienna, Austria) were applied for analysis.

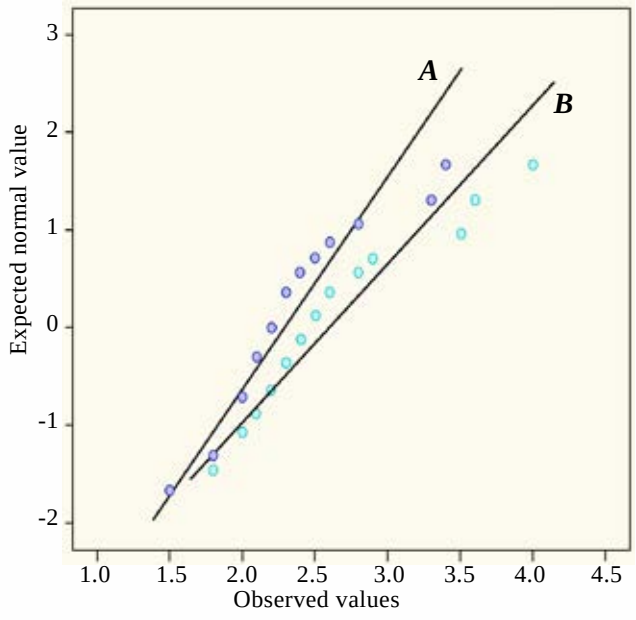

FIGURE 1. *Skewed distribution of the outcome values in group 1: A – before, B – after using experimental toothpaste.*

RESULTS

The study was conducted from November 2020 to March 2021.In general, after the usage of the experimental toothpaste in I group, there was an increase in the volume of saliva compared to baseline period (Fig. 2), while in II group there were no differences in the evaluated outcome at the two time points of the study.

In I group at baseline, the volume of saliva ranged from 1.5 to 3.4 *ml*, with a median value of 2.2 (2.0-2.48). The data changed in the direction of increase at the end of the study: fluctuations from 1.8 to 4.0 ml, the median accounted for 2.45 (2.2-2.88).In II group, there was no marked change in the amount of saliva separated in patients with xerostomia before and after the course of using the tested toothpaste: 2.35±0.5 and 2.35±0.45 respectively. Measurements of the outcome in this group ranged from 1.4 to 3.4. Note that in the control group, the range of values was from 4.4 to 5.0 *ml*, while the median level was 4.8 (4.6-5.0).

The study design involved both "before-after" comparisons, and the comparison of all the three groups with each, which is described in detail below. In I group, after the completed course of using the toothpastes (Fig. 3), we revealed statistically significant differences in outcomes compared

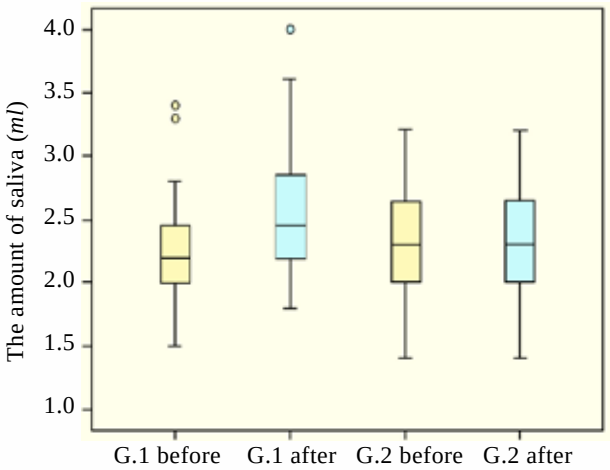

FIGURE 2. *Change in the amount of saliva in the comparison groups.*

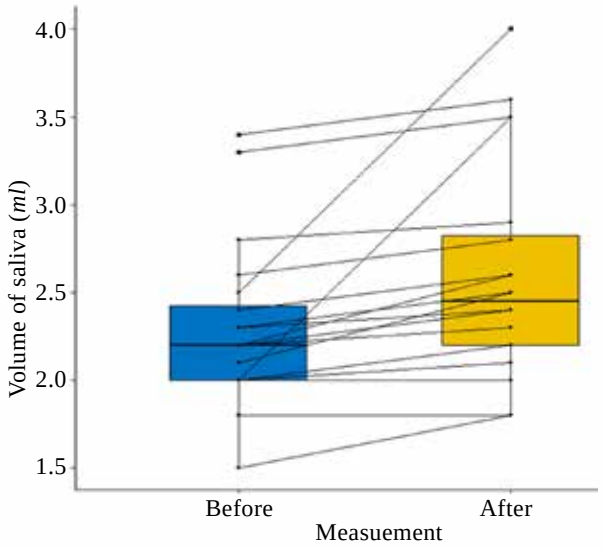

Figure 3. *A general trend in dryness of oral cavity in group 1 (black dots and straight lines denote data for individual patients).*

to the baseline period (Z=-3.77; p<0.0001). A directly opposite situation was observed in II group (p=0.1 period before *vs.* period after).

When comparing the groups with each other, the following was established. Before using the experimental toothpaste I and II groups did not differ significantly (the mean rank for I group 20.05; the mean rank for the second group 20.95; Mann-Whitney U-test=191.0; p=0.8).

After completing the treatment course, there were also no statistically significant differences between the compared groups (the mean rank for the first group 22.78; the mean rank for II group 18.23; Mann-Whitney U- test=154.5; p=0.8).At the same time, as can be seen on figure 4, the amount of saliva in I group was slightly higher

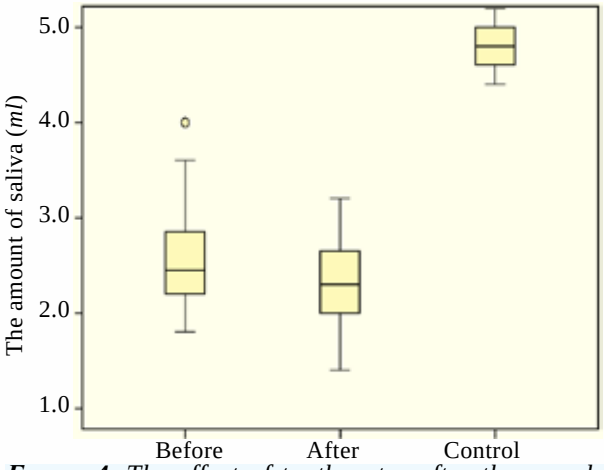

Figure 4. *The effect of toothpastes after the complete course (groups 1 and 2, the control group).*

(median 2.45) than in II group (median 2.3). This was although a remarkable result: even such a not very large difference in the measurements of saliva, according to the subjective feelings of the patients, apparently had a clinical significance.

For multiple comparisons, we used the Kruskall-Wallis test, followed by pairwise comparisons using the Mann-Whitney test (with an appropriate p-value correction). In general, there were statistically significant differences in the amount of saliva between the designated groups (chi2=40,238; p<0.0001). Both comparison groups significantly differed from the control group with respect to the amount of saliva (p<0.0001 in both cases) at the end of therapy. Having said that, I and II groups did not differ from each other (p=0.221).

Discussion

We performed a clinical and epidemiologic study which allowed evaluating the potential of using modern moisturizing multicomponent toothpastes in patients with signs of xerostomia who have undergone COVID-19. It was hypothesized that participants who underwent a complete course of a novel moisturizing toothpaste could benefit in terms of clinical improvement. Studying the effectiveness of such complex interventions as toothpastes is traditionally associated with certain methodological nuances that must be taken into account when developing a study design as well as a design of statistical analysis [*Furness S, 2011*].

This study has several strengths. First, we measure an outcome of interest (quantitative evaluation of excreted saliva) both in I group (experimental), as well as in the comparison II group in two periods, namely: before using of the tested toothpastes, and then again after the course of treatment. To ensure the possibility of establishing a causal relationship between the effect of moisturizing toothpaste and the severity of xerostomia, the study design implied a participation of a control group. The controlled nature of the study made it possible to adjust for the effect of changes in the patient's condition, which could occur over time.

Before-after design is known to be very efficient when immediate impact is to be studied and when relatively short courses of toothpaste are

used. In addition, the chosen study design avoided ethical difficulties that could potentially arise in randomized trials. We also note the relatively low cost, resource consumption, simplicity, as well as convenience for an individual and a researcher.

One inherent weakness of this study can be a high risk of selection bias which can affect the observed changes in measurements, due to the possible presence of unidentified differences between the compared groups. Another important limitation was the absence of randomization of participants, which may lead to confounding by indication. At the same time, we recorded a status of the patients before starting treatment, and we also made a comparison with the control group. Although we have tried to gather the necessary information on potential confounders, there might still be a risk of unidentified confounding. Within the posed research question, attempts were made to correct the effect which we observed from the use of the moisturizing toothpaste in terms of the regression to the mean.

Conclusion

The scientific community is facing with new challenges because of the ongoing spread of COVID-19 in many countries. There were numerous reports of the involvement of organs and tissues of oral cavity in the pathological process caused by infection with SARS-CoV-2 in humans. In this regard, the appearance of signs of xerostomia in patients can be of particular concern, which requires adequate management of such patients, complex treatment and effective hygiene measures. To the best of our knowledge this was the first study which provided preliminary results and demonstrated the therapeutic potential of the President PROFI AQUA Xerostomed® moisturizing toothpaste. Furthermore, we have outlined approaches to the construction of further clinical and epidemiological studies of effectiveness of interventions similar in nature. In turn, this will allow us to make more accurate and maximally unbiased judgments about prophylactic and therapeutic effects of such interventions.

REFERENCES

1. *Belchior Fontenele MN, Pedrosa MDS (2021).* Xerostomia and taste alterations in COVID-19. Ear Nose Throat J. 100(2): 186S-187S
2. *Biadsee A, Biadsee A, Kassem F, Dagan O., et al (2020).* Olfactory and oral manifestations of COVID-19: sex-related symptoms-a potential pathway to early diagnosis. Otolaryngol Head Neck Surg. 163(4): 722-728
3. *Chen L, Zhao J, Peng J, Li X, Deng X., et al (2020).* Detection of 2019-nCoV in saliva and characterization of oral symptoms in COVID-19 patients. Cell Prolif. e12923
4. *Fantozzi PJ, Pampena E, Di Vanna D, Pellegrino E., et al (2020).* Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19. Am J Otolaryngol. 41(6): 102721
5. *Farshidfar N, Hamedani S (2021).* Hyposalivation as a potential risk for SARS-CoV-2 infection: Inhibitory role of saliva. Oral Dis. 27(3): 750-751
6. *Freni F, Meduri A, Gazia F, Nicastro V., et al (2020).* Symptomatology in head and neck district in coronavirus disease (COVID-19): a possible neuroinvasive action of SARS-CoV-2. Am J Otolaryngol. 41: 102612
7. *Furness S, Worthington HV, Bryan G, Birchenough S., et al (2011).* Interventions for the management of dry mouth: topical therapies. Cochrane Database of Systematic Reviews. 12: CD008934
8. *John Hopkins' COVID map (2021).* https://origin-coronavirus.jhu.edu/map.html. Date of access: 13 April, 2020.
9. *Jothimani D, Kailasam E, Danielraj S, Nallathambi B., et al (2020).* COVID-19: Poor outcomes in patients with zinc deficiency. Int J Infect Dis. 100: 343-349
10. *Makedonova JuA, Porojskij SV, Gavrikova LM, Afanas'eva OJu (2021).* [Manifestation of diseases of the oral mucosa in patients who have undergone COVID-19] [Published in Russian]. Vestnik Volgogradskogo gosudarstvennogo medicinskogo universiteta. 1(77): 110-115
11. *Makeeva IM, DoroshinaVJu, Arakelyan MG (2013).* [Xerostomia and means that facilitate its manifestations] [Published in Russian]. Journal of Dentistry. 5(92): 12-13
12. *Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C., et al (2021).* Post-acute COVID 19 syndrome. Nat Med. 27(4): 601-615

13. *Omezli MM, Torul D (2021).* Evaluation of the xerostomia, taste and smell impairments after COVID-19. Med Oral Patol Oral Cir Bucal. 27: 24510

14. *Saniasiaya J (2021).* Xerostomia and COVID-19: unleashing Pandora's Box. Ear Nose Throat J. 100(2): 139S

15. *Satygo EA, Bakulin IG (2021).* [Clinical and microbiological signs of oral candidiasis in patients with COVID-19 receiving various pathogenetic therapies and having different levels of oral hygiene] [Published in Russian]. Parodontologija. 26(1): 4-8

16. *Sinjari B, D'Ardes D, Santilli M, Rexhepi I., et al (2020).* SARS-CoV-2 and Oral Manifestation: An Observational, Human Study. J Clin Med. 9(10): 3218

17. *Sugihartono T, Arafah N, Yamaoka, Miftahussurur M (2020).* Gastrointestinal manifestations in COVID-19 infection. The New Armenian Medical Journal. 4(14): 70-81

18. *Vogel-González M, Talló-Parra M, Herrera-FernándezV, Pérez-Vilaró G., et al (2021).* Low zinc levels at admission associates with poor outcomes in SARS-CoV-2 infection. Nutrients. 13: 562

19. *Wang C, Wu H, Ding X, Ji H., et al (2020).* Does infection of 2019 novel coronavirus cause acute and/or chronic sialadenitis? Med. Hypotheses. 140: 109789

20. *WHO (2021).* https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

21. *Xu H, Zhong L, Deng J, Peng J., et al (2020).* High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 12: 8

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