

World Overview of Xerostomia Therapeutics: Clinical Trials Analysis

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Abstract: Xerostomia is defined as the subjective sensation of dry mouth. Because it affects various systemic functions, it becomes relevant to research the therapeutic possibilities so that appropriate treatment can be indicated. Thus, this study aims to discuss the therapeutic possibilities for xerostomia treatment and analyze the most studied in clinical trials conducted worldwide. This descriptive exploratory study was conducted through a data analysis of clinical trials conducted worldwide for the treatment of xerostomia registered in the online platform "clinicaltrials.gov". The research was conducted during May 2019. Initially, 234 studies were identified, of which 97 corresponded to interventional clinical studies that addressed therapies for xerostomia. These surveys were recorded from December 1999 to May 2019. The 97 papers reporting treatments for xerostomia included various therapies such as mechanical and taste stimulants, pharmacological interventions, salivary substitutes, natural products, and alternative treatments. Among the researches analyzed, it was concluded that the most studied therapies for xerostomia worldwide were interventions using chewing gum, pilocarpine, biotene spray, honey mouthwash, conventional acupuncture and salivary gland transfer.

Keywords: Clinical Studies, Treatment, Xerostomia.

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I. Introduction

Xerostomia is characterized by the subjective sensation of dry mouth, which may result from low saliva production, which most often results from salivary gland hypofunction, but may also be present in individuals with normal salivary flow due to changes in composition of saliva. Its etiology is multifactorial and may be caused by changes in the salivary glands, or as a result of imbalance or systemic changes ^{[1][2][3][4]}.

Because it is a symptom that affects approximately 20 to 30% of the world population, xerostomia, which can be reported as transient or permanent, according to its intensity, provides functional and / or social limitations that reflect in the reduction of the quality of life. Some patients with chronic dry mouth may be at greater risk of psychological distress, such as depression ^{[5][6]}.

Saliva acts as a protector in the oral cavity, fulfilling the functions of maintaining balance in digestion, taste and speech. It is produced almost entirely by the submandibular, sublingual and parotid glands, and provides important buffering capacity in caries prevention, remineralization, antibacterial activity, tissue repair, and acts as a lubricant and humidifier of the oral mucosa. Causing a great impact on the patient's quality of life when there is a reduction in their production ^{[7][8][9]}.

Older age has been exposed as a risk factor for xerostomia, because although salivary flow does not necessarily decrease with increasing age, older people are more likely to suffer from dry mouth due to the increased prevalence of chronic diseases and their associated pharmacological treatments. In addition, diseases such as diabetes mellitus type II, AIDS, Sjögren's syndrome; as well as head-and-neck radiotherapy, as well as several classes of drugs are also recognized as important associations of dry mouth ^{[1][10]}.

Given the negative impact that xerostomia causes, it is important to treat it in order to restore the quality of life of patients and homeostasis of the body, since it affects various systemic functions. Several therapeutic resources can be used and must be defined by the ability or not to produce saliva. Given this relevant scenario, the importance of studying the therapeutic possibilities for the treatment of xerostomia is justified according to the various aspects involved ^{[11][12][13][14]}.

The aim of this study was to analyze the therapies for the treatment of xerostomia used in clinical trials performed worldwide.

II. Materials and methods

Exploratory descriptive study, conducted through a data search referring to clinical studies conducted worldwide for the treatment of xerostomia. For this, an analysis of the clinical trials registered in the online platform "clinicaltrials.gov" was performed using the descriptors "treatment" and "xerostomia". These descriptors were associated by the platform with the descriptors "therapy", "dry mouth" and "administration". The survey was conducted during May 2019.

The inclusion criteria was based on the selection of interventional clinical studies that addressed therapies for xerostomia. While the exclusion criteria were observational studies, and interventionists who were not associated with specific treatments for the xerostomia condition.

III. Results and discussions

Analyzing and studying the various therapies for xerostomia is of extreme importance. This condition is characterized by the subjective sensation of dry mouth, of multifactorial etiology, and may be due to pathologies, treatments or changes in saliva production by salivary glands impacting on quantity and / or quality. It is a complex problem, with consequences for both oral and general health of affected individuals, which can trigger physical, emotional, social and psychological changes, compromising the quality of life. Due to the multiplicity of problems, this condition must be carefully considered by health professionals, so that complications are prevented and the dignity of individuals is preserved. Therefore, it is important to know the existing therapies so that they can intervene in a convenient and competent manner^{[15] [16] [17] [18] [19] [20] [21]}.

In the clinicaltrials.gov online platform, in May 2019, 234 registered studies were identified. However, 97 were selected that corresponded to interventional clinical studies that addressed therapies for xerostomia. These surveys were registered between December 1999 and May 2019. Among the countries that developed studies on this theme, it can be highlighted the United States, France, China, Brazil and Canada, which presented the largest number of works registered on this theme, respectively.

There are several clinical studies registered in this platform, including the interventional ones, in which volunteer human beings are submitted to health interventions, whether they are led by drugs or not, where the uses of the therapies, their reactions, their behaviors and their later use according to its effects will be tested. When such studies are well conducted, they are of wide relevance because they provide results that serve as parameters for daily clinical practice and for health researchers, providing knowledge to the different groups that seek them, enabling access, as it centralizes research from around the world, reduces systematic errors and distortions regarding research and its results, and presents possibilities for innovative research^{[22] [23] [24] [25]}.

The therapeutic possibilities presented in these selected studies are conducted depending on the various etiologies regarding the condition of xerostomia, such as iatrogenesis (head and neck radiotherapy, use of cytostatic substances, bone marrow transplantation, smoking, alcohol consumption, drug use and polypharmacy); organic diseases (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, type 1 and 2 diabetes mellitus, AIDS, hepatitis C, thyroid disease, infectious diseases (parotitis), menopause, psychiatric diseases, alzheimer's, among others); functional (dehydration or inadequate fluid intake, diarrhea, vomiting, protein deficiency, cardiac changes and malnutrition) and psychological (anxiety, stress and depression)^{[16] [20] [21] [26] [27] [28]}.

Relevant clinical trials worldwide are registered on the clinicaltrials.gov platform, which is an open access portal to clinical trial analysis results and patient outcomes, and is characterized as a database platform (commonly referred to as a "database"). records and results data"), managed / sponsored by private and public institutions around the world. It is made available to health professionals and academics, researchers, as well as patients and families. The site is maintained by the National Library of Medicine (NLM) and the National Institutes of Health (NIH), which are two of the most prominent North American healthcare institutions. The results of available studies are from research carried out in the 50 states of the United States and 210 other countries^[25].

In addition to interventional clinical trials, observational studies are also approved, in which the researcher does not interfere with exposure, and are performed in humans, evaluated in pre-selected groups, where only the behavior without medication is analyzed. volunteer patients; and Expanded Access Programs, which report the procedure for obtaining an experimental drug or device outside a clinical trial^{[22] [23] [24] [25]}.

Among the 234 studies, 137 were not included, among which 38 were observational studies, and 99 interventional clinical studies that, despite using the descriptors xerostomia and treatment, were associated with specific treatments for other conditions linked to the term xerostomia, such as treatment of joint problems, rheumatic diseases, systemic lupus erythematosus and dry eye associated with Sjogren's Syndrome, but were not specific treatments for xerostomia.

The 97 papers reporting treatments for xerostomia included various therapies such as mechanical and taste stimulants (chewing gums, oral gels, mouthwashes), pharmacological interventions (cevimeline, pilocarpine, amifostine), salivary substitutes (artificial saliva, sprays, oral gels), natural products (coconut oil,

honey, green tea pellets, dairy products), alternative treatments (conventional acupuncture, electrostimulation acupuncture, laser therapy, salivary gland transfer, sialendoscopy).

When checking the registered clinical studies, it is possible to notice the diversity of works developed in different regions of the world, observing different therapeutic profiles, which may be associated according to the preferences of certain study groups, related to the local reality of each country. Among these studies, in relation to mechanical and taste salivary stimulation therapies, the most prominent interventional clinical studies were chewing gum and were associated with xerostomia induced by radiotherapies.

Garcia et al. (2019) ^[29] reported that the use of chewing gum resulted in increased salivary volume (five studies), relief of xerostomia (seven studies) and reduced thirst (four studies). It was not possible to establish the number of gums per day, and it was often recommended to use as desired. There was a predominance of studies with dialysis patients and with oncological patients.

For pharmacological interventions, Pilocarpine (in various forms, such as tablets and sprays, being used in the therapy for radiotherapy-induced xerostomia and Sjogren's Syndrome), and Cevimeline pill, also for radiotherapy-induced xerostomia, were more prominent. Brimhall, Jhaveri and Yepes (2013) ^[8] compared Pilocarpine and Cevimeline-based drugs and found in their results that both medication treatments proved to increase salivary secretion, with no significant difference between pilocarpine and cevimelin. In addition, the perceived side effects between the two medications were similar. However, there was a slightly higher increase in pilocarpine saliva, but the difference was not statistically significant.

Among the registered clinical studies referring to interventions through salivary substitutes, there were found in greater number, trials using Biotene products, both in the form of mouthwashes and sprays, to treat xerostomia with etiology resulting from radiotherapies. Barbe et al. (2018) ^[30] addresses in their study the effectiveness of Biotene in improving oral health and the quality of life related to xerostomia. However, he points out that such therapy does not completely replace continuous saliva secretion in the mouth, and symptomatic relief is temporary.

For alternative treatments, larger amounts of clinical studies regarding acupuncture were obtained, such as therapy for xerostomia induced by radiotherapy and / or Sjogren's Syndrome, used in conventional and electrostimulation forms. Homb et al. (2014) ^[31] conducted a retrospective study with 16 xerostomia patients to evaluate the effect of the combination of acupuncture (manual, auricular and electroacupuncture) on the dry mouth problem in relation to radiation-induced xerostomia, which resulted in a significant improvement. Dry mouth and pain during the initial six weeks of treatment, being reduced by 35% and 50%, respectively. These effects continued after six weeks, concluding that the combination of acupuncture considerably decreases the severity of dry mouth and pain with lasting effects.

Salivary Gland Transfer (SGT) surgery (in cases of pre-radiotherapy or with radiotherapy already in place) consists of moving a salivary gland out of the radiation-affected area to protect it from the side effects of RT, thus preventing Xerostomia ^[32], was also an alternative treatment widely found in the registered trials. Sood et al. (2014) ^[33] performed a systematic review and meta-analysis to verify the efficacy of SGT in preventing xerostomia and maintaining salivary flow rates after treatment with radiotherapy in 177 patients. They obtained results showing that TGS prevented radiation-induced xerostomia in 82.7% of patients, and that after 12 months of RT, unstimulated and stimulated salivary flow rates were increased to 88% and 76%, respectively. Compared to the control group, 12 months after RT, rates were significantly higher in patients with SGT, concluding that this therapy appears to be highly effective in preventing xerostomia in patients receiving head-and-neck radiotherapy.

Among the natural products, it can be highlighted, interventional clinical studies that used pure honey as a mouthwash in cases of xerostomia of radiation etiology, and also due to radioiodine therapy for thyroid cancer. Charalambous et al. (2017) ^[34] demonstrate in their study that thyme honey has positive effects on the management of radiation-induced xerostomia in cancer patients.

Given the results obtained, it can be noticed the relevance of studying the clinical research developed worldwide, considering the existence of several therapeutic possibilities for xerostomia, according to its etiology, and depending on the patient's condition on the ability to stimulation of salivary glands to produce saliva.

IV. Conclusion

It can be concluded that among the therapies for xerostomia used worldwide according to clinical studies registered in the clinicaltrials.gov online platform, were found therapies with mechanical and taste salivary stimulants, pharmacological interventions, salivary substitutes, natural products and alternative treatments, with emphasis on interventions related to chewing gum, pilocarpine, biotene spray, honey mouthwash, conventional acupuncture and salivary gland transfer, respectively, due to greater approaches in interventional clinical trials.

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