Update on xerostomia: Current treatment modalities and future trends

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This article discusses some of the current treatment modalities available to those who suffer from xerostomia and looks at some therapies currently being explored to ameliorate the condition. With the number of elderly patients in the U.S. population expected to increase—concomitant with the increase in incidence of xerostomia in this group as well as other special patient population groups (that is, postradiation, Sjogren's syndrome, and so forth)—it is increasingly important that dentists maintain an awareness of the clinical implications of xerostomia and a knowledge of appropriate treatment recommendations.

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Xerostomia (or the clinical perception of dry mouth) is related to a number of chronic conditions and diseases. These include patients who are taking multiple medications (polypharmacy) as well as those undergoing radical radiotherapy for treatment of head and neck neoplasms and other disease processes, including uncontrolled diabetes, sarcoidosis, systemic lupus erythematosis, and the autoimmune exocrinopathy Sjogren's syndrome.[1-4] Although xerostomia can affect a person at any age, it is more likely to occur among the elderly, as this group is at an increased risk for one or more of the aforementioned conditions.

It currently is estimated that approximately 30% of persons over the age of 65 are affected by xerostomia.[1] Its clinical course can range from mild to moderate to severe. A number of negative sequelae usually occur in those with the condition; these include dysphagia, dysgeusia, difficulty in speaking, severe oral discomfort, an increase in the rate of decay and recurrent decay, a decrease in the retention of prostheses (that is, maxillary dentures), and an increase in opportunistic infections such as oral candidiasis.[3,5]

Current treatment modalities

A large number of treatment options are available for patients who suffer from xerostomia; these generally are prescribed based on the etiology. For example, a number of palliative treatment options are available for xerostomia secondary to permanent destruction of the parenchymal acini, as usually results from radiotherapy for head and neck cancers or in primary Sjogren's syndrome. Conventional methods include frequent sipping of water and the application of various types of mouth rinses, sprays, and gels. Many such products have become available on the market; some of them have been studied through clinical trials.

Utilizing patients who either tested positive for primary Sjogren's syndrome or had undergone postradiation treatment for head and neck cancer, a 2000 study evaluated the effectiveness of a commercially available oral moisturizer (Optimoist, Colgate-Palmolive, Canton, MA; 800.763.0246) on salivary flow rate, patient-reported symptoms of dry mouth, oral pH, oral microflora (*Candida* and *Lactobacilli* species), and swallowing.[6] The patients were instructed to use Optimoist for two weeks; at that time, a subjective and objective analysis of its effectiveness was measured. Results showed significant improvements in whole unstimulated salivary flow rate (from 0.115 mL/min to 0.237 mL/min), a decrease of *Candida* colonization (in 43% of subjects), and a subjective improvement of xerostomia in 58% of subjects.

In a phase II clinical trial of post-treatment radiation patients using Biotene products (Dry Mouth Toothpaste, Gentle Mouthwash, Dry Mouth Gum, and Oral Balance Gel; Laclede Co.; Rancho Dominguez, CA; 800.922.5856), subjective improvements were found regarding patient's intraoral dryness (54% of patients), ability to eat (46%), and oral discomfort (61%); by comparison, 36% of patients reported major improvements in intraoral dryness, while 25% reported major improvements in their ability to eat and 43% reported major improvement in oral discomfort.[7]

Using a double-blind, crossover clinical study, Epstein et al evaluated the efficacy of Biotene Dry Mouth Toothpaste and Oral Balance Gel in reducing the complaints of xerostomia among a group of patients who had received radiation for head and neck cancer.[8] The study found an overall improvement in subjective complaints, reaching statistical significance ($p = 0.08$). The toothpaste, mouthwash, chewing gum, and gel that Biotene produces all contain lactoperoxidase, lysosyme, and lactoferrin, three components that occur naturally in human saliva. These products also include xylitol, a nonfermentable alcohol sugar. The combination of these ingredients may make these products effective anticariogenic agents.[9]

In addition to palliative therapy associated with permanent destruction of salivary acini, other forms of treatment—both local and systemic—have been used to induce secretions from remaining salivary gland tissue. The two most common systemic agents available by prescription are the secretogogues pilocarpine HCL (Salagen, MGI Pharma Inc., Bloomington, MN; 800.562.5580) and cevimeline HCL (Evoxac, Daiichi Pharmaceutical, Montvale, NJ; 877.324.4244), both of which are believed to act on the muscarinic receptors in the salivary glands.[10] Pilocarpine has been well-studied in controlled trials and has demonstrated significant improvement in symptoms associated with dry mouth.[11] Although pilocarpine has been proven effective, there also have been some mild, adverse common side effects associated with it, such as excessive sweating, gastrointestinal (GI) disturbance, increased pulmonary secretions, bradycardia, tachycardia, blurred vision, and excessive sweating, which is reported as the most common side effect.[12] Most of these side effects are reported to be rare.

Cevimeline HCL is purported to offer the same amount of relief from symptoms of dry mouth as pilocarpine, with fewer side effects.[10] This reaction appears to be due to the drug's higher affinity to the M3 sub-receptor type (40x higher than pilocarpine HCL), which is specific to salivary gland tissue. By contrast, pilocarpine has an equal affinity for M1 and M2 receptors, which are located in the GI tract and cardiac tissue. Both drugs are contraindicated in patients who are positive for narrow-angle glaucoma.

Bethanechol and anethol trithione are other medications that appear to act via the parasympathetic system.[10] Bethanechol normally is used for urinary retention and neurogenic atony of the bladder and has led to modest improvement in subjective symptoms associated with dry mouth; however, the current studies available have shown this improvement only among individuals whose dry mouth was related to radiation therapy.[13] Anethol trithione normally is used for stimulating bile, although it also has been used as a sialogogue. Studies on this drug also were carried out among populations of patients who were on multiple medications, with significant improvements noted.[14] According to Schiodt et al, the drug does not improve xerostomic conditions related to Sjogren's syndrome.[15] The most common side effect from this drug was GI upset with flatulence.[15]

Other forms of therapy intended to induce remaining salivary gland secretions have included chewing gum and lozenges of various types. Stewart et al tested two types of chewing gum and a sour lemon lozenge in post-treatment radiotherapy individuals who were positive for Sjogren's syndrome and found no statistically significant improvement in salivary stimulation.[16] More recently, a randomized, double-blind, placebo-controlled study administered interferon-α lozenges to Sjogren's syndrome patients for a period of 24 weeks and found statistically significant improvement in salivary flow and subjective improvement in symptoms of dry mouth and dry eyes.[17]

Future trends

Novel approaches for treating xerostomia currently are being investigated. Some of the more recent methods have included therapies such as acupuncture and acupuncture-like transcutaneous electric nerve stimulation (TENS). Both of these methods rely on certain trigger points in and around the head and neck region, with the goal of stimulating the parasympathetic innervation of salivary gland tissue (cranial nerves IV and VII). Acupuncture accomplishes this task through a series of injections with small needles of varying sizes. Acupuncture-like TENS accomplishes the same objective without the use of needles.

The first report of acupuncture for xerostomia treatment appeared in 1981.[18] Since then, observational studies have reported an increase in salivary flow rate among both diseased and healthy individuals treated with this method. In a 2000 study, Blom et al reported that the effects of acupuncture provided relief for individuals positive for Sjogren's syndrome and postradiation patients and continued to provide relief for up to six months post-treatment.[19] A separate study in 1999 noted that the use of acupuncture increased the amount of calcitonin gene-related peptide (CGRP) in saliva.[20] CGRP is thought to affect salivary flow positively and provide positive trophic effects on the oral mucosa.

Acupuncture-like TENS also has been shown to be effective. In a 2003 phase I-II trial, Wong et al used a method termed *Codetron* to deliver electronic nerve stimulation (similar to those delivered by conventional acupuncture methods) twice per week for six weeks.[21] Patients with symptomatic xerostomia from radiation therapy and evidence of residual salivary function were recruited into the study. Results showed statistically significant improvements in both salivary flow rates and subjective complaints of dry mouth for up to six months after treatment.[18] A phase III study with controls is planned to confirm these findings.

Gene transfer (recombinant DNA technology) and guided tissue regeneration (GTR) are two new areas of exploration that could affect restoration of function to damaged salivary parenchyma. Gene transfer uses a vector to transfer the gene encoding of a specific functional protein. This protein is inserted into the ductal cells of salivary glands, causing them to secrete. Ductal cells normally are impermeable to water; as a result, they are incapable of producing saliva. These cells become active upon insertion of the human aquaporin-1 (hAQP1) gene. Various types of viral vectors have been used; however, recombinant adeno-associated virus 2 (rAAV2) appears to have the greatest specificity for the ductal cells. Initial studies transfected postirradiated rats with the rAAV2 virus carrying the aquaporin gene, reporting an increase in rates of submandibular gland secretion.[22] Subsequent studies were conducted on rhesus monkeys using the same experimental model of transfection; however, the results from that study were not as successful, with only half of the experimental group showing improved rates of salivation.[23] It has been stated that additional work is needed to find an ideal viral vector that would have properties of specificity for cell type and the ability to carry the necessary amount of genetic information, as well as one that does not elicit any type of immune response.[22]

GTR has been used for a number of dental and nondental procedures; the possibility of using it in salivary gland replacement therapy is being explored. The main objective of GTR is to replace tissue that has been lost through disease processes. Joraku et al demonstrated the feasibility of using GTR to create functional salivary gland tissue.[24] Investigators removed functional salivary tissue from human subjects and processed the tissue using an explant procedure. The tissue samples were sectioned into fragmented pieces, seeded on a polyglycolic acid polymer scaffold, and implanted subcutaneously in athymic mice. Nonseeded scaffolds were used as controls. Samples were obtained for phenotypic and functional analysis at two, four, and eight weeks. A combination of immunohistochemical and western blot techniques was employed to check the seeded tissue for expression of alpha-amylase, aquaporin-5, and cytokeratins; results revealed functional expressions of these constituents at each time interval.[21]

In 2004, Aframian et al examined the possibility of using salivary gland acini to develop an artificial type of salivary gland.[25] Cultures of submandibular salivary gland cells were harvested and seeded on a bed of irradiated NIH 3T3 fibroblasts, which served as a feeding layer. Upon examination, the cells demonstrated many characteristics of normal functional salivary tissue and aligned themselves in the same orientation as salivary gland acini (that is, side by side, with tight junctions on the basolateral side of each cell's membrane). It was suggested that an artificial salivary gland could be constructed by using this method to acquire functional salivary gland cells.[22]

Summary

Xerostomia is a condition that currently has no definitive means for treatment. A number of palliative and inductive treatment methods appear to be effective for reducing the morbidity associated with this condition; however, many of the current treatment options that are available are merely transient and as such are not considered to be a satisfactory treatment option.[24-26] Advances in gene therapy and GTR offer hope for curative-type treatment in individuals who are xerostomic secondary to loss of functional gland tissue.

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