HYPOSALIVATION/XEROSTOMIA

Management of Hyposalivation and Xerostomia: Criteria for Treatment Strategies

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Abstract: Saliva management in patients with hyposalivation is potentially complex. Future development of oral care products and treatment strategies requires attention to the biology of saliva and the best means of providing a continuum of relief for people with xerostomia—the sensation of dry mouth—and hyposalivation—documented reduction in saliva flow. Improvement in patient care requires that clinicians be aware of approaches to management, desirable qualities of methods and products, and that they seek the development of products that support the functions of saliva and promote comfort and health. In this brief review of the epidemiology of hyposalivation, the biology and functions of saliva are presented in order to guide clinical decision-making to address the needs of patients with dry mouth.

Saliva supports the health of the oral environment and oral function in communication, eating, clearing the oral cavity, and swallowing. It hydrates, maintains, and lubricates oral soft tissue, and supports mineralization of teeth, reduces infection and promotes healing and maintenance of oral mucosa. It is for these reasons, xerostomia and hyposalivation—both of which are common conditions—can greatly impact quality of life as well as oral and, potentially, systemic health.

The complex functions of saliva may be maintained in patients with hyposalivation if adequate stimulation of residual function is possible. However, when saliva stimulation is not sufficient, the goals of therapy—which may include use of long-acting topical products—would be to provide: saliva enhancement; surface wetting; lubrication; tissue hydration, dental mineralization; impact on oral flora; and clearance of saliva from the oral cavity.

Biology of Saliva

Saliva is a complex biologic fluid with multiple functions (Table 1 and Table 2). The principle goal of management of xerostomia is to provide symptomatic care on an ongoing 24-hour basis and, in the case of concomitant salivary gland hypofunction, to address the loss of important biologic functions of saliva.

Saliva is subject to diurnal variation, with reduction in saliva at night; dry-mouth complaints may be aggravated during extended-time speaking and at night, causing a disturbed sleep pattern. Salivary glands are in a resting state for most of a 24-hour day, with a continuous relatively low flow rate induced by autonomic activity (sympathetic and parasympathetic nervous regulation), while the stimulated state is present for only a few hours in relation to masticatory and/or gustatory stimulation with up-regulation of parasympathetic stimulation. Thus, the resting state has the highest

TABLE 1

Biologic Functions of Saliva

Surface wetting, diluting, clearing, facilitating taste, bolus formation
Lubrication (mucin): speech, swallowing, prosthesis function
Barrier function (mucin, wetting)
Mucosal protection: growth factors, (mucin), hydration
Facilitating mucosal maintenance, regeneration, and repair
Antimicrobial effects: innate, acquired
Adherence, clearing, antimicrobial factors (polypeptides, defensins, enzymes, etc), antibodies
Dental hard tissue maintenance: pH, remineralization, diluting, clearing
Other: Initiate digestion, social role; texture/viscosity; clearing medications (saliva secretion, swallowing)
Sensory/subjective functions of saliva:
Wetting, comfort, thirst, mucosal sensitivity, facilitating taste, swallow function, speech

impact on overall xerostomia, general oral well being, and the oral condition. Resting saliva is composed primarily of mucinous secretion from the submandibular, sublingual, and minor salivary glands, with a limited serous component.

The minor salivary glands contribute 70% of the total amount of mucins in whole saliva while only contributing 10% of the fluid secretion. Mucin appears critical in the mucosal barrier, lubrication, and forming the salivary pellicle on teeth. Stimulated saliva is largely made up of serous secretions primarily from the parotids, which are increased with chewing and eating; it contributes a total of 50% of the stimulated whole-saliva volume, while the parotids contribute 20% during rest.

In addition to salivary volume, texture and viscosity are critical concerns frequently not considered in the clinical setting. For example, during head and neck radiation therapy, reduced serous secretion may lead to an increase in mucinous viscous saliva, which can be difficult to manage, may aggravate nausea, and can sometimes be associated with greater complaints than reduction in overall secretions that may follow continuing cancer care. In addition, excessive mucin may be difficult for the patient to manage and may be of increased concern at night, thereby affecting sleep. This aspect of salivary gland dysfunction is occasionally addressed by use of mucolytic drugs; however, currently available products have limited efficacy and further development is needed.

Patient Report

A patient presented with xerostomia, hyposalivation, and excessive mucin following intensity-modulated radiation therapy for cancer of the left maxillary sinus. Although the mucositis resolved, the patient had persistent severe xerostomia and hyposalivation with thickened secretions. Sialometry showed a resting whole-saliva flow rate of 0 ml/min and a stimulated whole-saliva flow rate of 0.20 ml/min. In some areas of the mouth and throat, the viscous saliva became crusts of dried salivary mucins, causing nausea and discomfort, which affected the patient's sleep.

The salivary gland dysfunction had caused extensive tooth damage due to mineral loss, cavitation, and chronic oral fungal infection. Quality of life was severely impaired due to the sensitive and dry mouth; loss of taste; impaired speech, chewing, and swallowing; and disturbed sleep. The patient was able to receive limited short-term relief by sucking on fluoride-containing tablets designed for dry-mouth patients. Due to tooth loss, chewing gum was not an option, and the patient disliked the taste and consistency of a gel product, which also caused nausea; the patient preferred to use water frequently applied by a spray bottle at 10-minute intervals. Available mucolytic drugs were ineffective.

Prevalence and Morbidity

Like the aforementioned patient, there are many people affected by xerostomia and salivary gland hypofunction (Table 3). It has been estimated that up to 20% of a population-at-large suffer from xerostomia,[1] which is the subjective sensation of dry mouth. It is distinct from salivary gland hypofunction, which is objectively decreased volume of secreted saliva, and hyposalivation, which is defined as a pathologic reduction in salivary secretion (≤ 0.1 ml/min for resting whole saliva and/or ≤ 0.7 ml/min for stimulated whole saliva)[2]; furthermore, reduction in saliva from prior levels not necessarily below these thresholds may result in negative health outcomes. It is important to note that while they are often correlated, salivary gland hypofunction and xerostomia are not always related. For example, over time, patients with hyposalivation may become accustomed to the reduced saliva production and report less concern with xerostomia; however, oral complications of hyposalivation can continue. Also, patients may report xerostomia with normal quantity of saliva production, which may represent changed composition of saliva—eg, lubricating proteins, or mucosal sensory change such as in some cases of burning-mouth syndrome. Therefore, in evaluation of saliva and its multiple functions, both subjective and objective saliva evaluation may be required.

TABLE 2

Impact of Salivary Dysfunction

Symptoms:
Dry mouth (xerostomia)
Dysphagia
Dysphonia
Odynophagia
Altered/reduced taste
Mucosal sensitivity/burning sensation
Difficulty in wearing dentures
Local disease:
Dental demineralization/caries
Dental erosion
Dental hypersensitivity
Halitosis
Atrophic and red oral mucosa
Traumatic mucosal ulceration
Cracked lips
Angular cheilitis
Microbial shifts: candida infection, gingivitis, periodontitis, other pathogens
Systemic impact:
Pharyngitis/laryngitis
Acid reflux/esophagitis
Dietary accommodations/nutritional intake
Infection
Social impact–social and role function:
Speech, taste, diet, pain
Impaired quality of life

Symptom Management Considerations

The ideal products and protocols for management would provide a continuum of care 24 hours a day. Due to the lubricating and

TABLE 3

Populations At-Risk for Hyposalivation

Medication-related
Diabetes mellitus
Autoimmune
Sjögren's syndrome
Connective tissue disease, eg, systemic lupus erythematosus
Graft-versus-host disease (allogeneic hematopoietic stem cell transplantation)
Cancer therapy populations
Head and neck cancer: radiation, chemotherapy, targeted therapy
Hematopoietic cell transplant, total-body irradiation
Radioactive iodine for thyroid cancer
Solid tumor: chemotherapy, targeted therapy
Renal dialysis patients
Elderly (many due to medications)
Terminally ill patients
Miscellaneous salivary gland diseases

TABLE 4

Ideal Functional Impact

Oral and dental health
Reducing risk of infection:
Antimicrobial
Promotion of oral and oropharyngeal function:
Taste, dysphonia, dysphagia, odynophagia
Barrier function, promotion of wound healing:
Coating and pain relief
Anti-inflammatory and growth factors:
Mucositis
Immune-mediated inflammatory oral mucosal disease
Acute wound healing (trauma, surgery)
Chronic wound healing (necrosis)

protective properties of saliva, patients benefit most from stimulation of a residual secretory capacity; therefore, enhancement of saliva flow rate by taste, texture, and sialagogue effect are of importance. However, if the salivary glands cannot be adequately stimulated, replacing the functions of adequate saliva production is sought.

Lubrication and wetting must be provided to the oral cavity by sipping or spraying water, or using oral rinses or gels. This function is facilitated by substantivity of the product and duration of retention in the mouth. Thus, the ideal products and management protocols vary individually; they depend on the cause of salivary gland hypofunction—whether due to inhibition of salivary gland secretion or destruction of gland tissue—and individual patient preferences of application, texture, and flavor.

Also, due to the diurnal variation and patients' lifestyle habits, the need for relief may vary during the day, and different products or formulations may be helpful at different times of the day. For example, oral rinses, lozenges, or chewing gum may assist when awake, but longer-duration products such as an oral gel or molecular enhanced substance may be more helpful at night. This may also vary with the severity of salivary gland hypofunction—that is, stimulation of secretions may be possible in mild to moderate salivary gland hypofunction, but not when hyposalivation is severe. Furthermore, the texture and viscosity of the palliative product may be poorly tolerated by people with essentially no saliva production, compared to those with some production. In addition, patients with hyposalivation often suffer from reduced or altered taste sensation; therefore, because many patients are dependent on the use of dry-mouth products on a 24-hour basis, sometimes indefinitely, it is desirable that a variety in taste modalities of dry mouth products is available to meet individual patient preferences and the need for variation during each day.

Care of patients with hyposalivation may be best managed by preventive (regular schedule) surface-wetting, cellular hydration, with "breakthrough" use of convenient products (eg, oral spray, gel product, lozenge, chewing gum) when dry mouth is increased, such as before social engagements and speech making. Enhanced mineralization of tooth structure and antimicrobial effects are critical functions of saliva and important in any strategy for management of hyposalivation.

Controlled treatment trials are required in various populations with differing etiologies of hyposalivation and varying degrees of dry mouth—eg, with/without saliva production. Patient evaluation should employ standard tools for assessing saliva dysfunction, such as the Vanderbilt Head and Neck Symptom Survey (for oral dryness, dysphagia, and dysphonia)[3,4] or the simple assessment suggested by Fox et al.[5] Wetting of mucosa and determining the presence or absence of the salivary pool are rapid clinical assessments that are easily performed[6]; and measurement of salivary secretion at rest and during stimulation can give objective measures of production. This is important both for professional assessment of the risk of oral complications of salivary gland dysfunction and being able to keep the patient informed about the severity of hyposalivation and the potential level of a stimulatory effect.

Further, the conditions more commonly seen due to hyposalivation should be assessed clinically. These include: dental decay (demineralization, caries); gingivitis and plaque levels; mucosal erythema; white plaques; and cracking at the corners of the mouth, which may be associated with Candida infection. Considerations should include: lip care; care of oral and oropharyngeal regions with goals of surface wetting, comfort, lubrication, hydration; impact on oral and pharyngeal function; and periodontal and dental disease prevention, including mineralization of teeth. Also, products for management of the other oral complications induced by hyposalivation should be directed towards this particular patient population's needs—eg, avoidance of strong flavors (such as menthols) and detergents in toothpaste; thus, it would be desirable to have high-dose fluoride toothpastes specifically prepared for dry-mouth patients

with vulnerable oral mucosa, sugar-free topical antifungal treatments, and non-alcohol-based antiseptic mouthwashes. Attention should also be given to the pH of a product and avoiding an acidic pH.

Approaches to Management

Whenever possible, salivary stimulation should be provided when residual function remains. When residual function is present, salivary stimulation may be increased by taste (flavor), lozenge/tablet dissolved in the mouth, chewing, and biologically by systemic medications.

Systemic prescription medications with stimulatory effect on salivary glands include pilocarpine, cevimeline, and bethanechol. Pilocarpine is a cholinergic parasympathomimetic agonist with mainly non-selective muscarinic action, but it also has mild beta-adrenergic activity. Cevimeline is a cholinergic agonist, and bethanechol is a carbamic ester of β-methylcholine that is resistant to degradation by cholinesterase; both have a high affinity for muscarinic M3 receptors, which are predominantly present in salivary gland cells. Thus, cevimeline and bethanechol may have less pronounced systemic adverse effects. Nevertheless, currently available pharmacologic stimulation of salivary glands may result in systemic adverse effects that limit use in some patients.

Along these lines, a less explored field is topical pharmacologic stimulation of the salivary glands, which could provide treatment options with a higher comfort level to patients. Other approaches that have received initial study include acupuncture, electrostimulation (provided by an electric circuit imbedded in an acrylic dental splint), incorporation of saliva substitute reservoirs into intraoral devices, and low-level light (laser) therapy. However, in many people, increased saliva production is not possible or insufficient, and local products are used for mouth wetting and preventive/treatment strategies for oral and dental disease should be instituted.

Commercially available saliva substitutes have been developed with constituents designed to resemble the physical properties of salivary glycoproteins (viscosity and moisturization), antibacterial components of saliva, and inorganic substances to retard enamel demineralization. The majority of these saliva substitutes are based on carboxymethylcellulose or mucin (Europe); many other formulas have been explored, such as hydroxymethylpropylcellulose, polyglycerylmethacrylat, polyethylenoxide, xanthan gum, linseed extract, aloe vera, emulsions, and a variety of oils. The major disadvantages of the saliva substitutes is their generally short duration of relief and the lack of biologic constituents.[7]

Implications for Product Development

Thus, there is a potential for improved topical therapy whose goals would include continuous moisturization, enhanced tissue hydration, provision of barrier function, microbial prevention, and dental mineralization (Table 4). Industry is encouraged to consider the multifaceted functions of saliva in symptom management and oral health, and to develop products with evidence of efficacy to remedy this poorly addressed and common patient need.

Desirable characteristics of products for local oral/oropharyngeal application are summarized in Table 5. The healthcare provider should be aware of the constituents and qualities of any medications and topical applications available, and should assess the evidence of effect and desirable qualities of the product before selecting it for use. Studies should be conducted: 1) in different at-risk populations; 2) in those with reduced saliva production; and 3) in those without functional production for whom the product may be considered, compared to placebo or control, in randomized blinded trials of adequate sample size and duration. In this way dentistry may be better able to address this prevalent oral care need that impacts oral and oropharyngeal function, quality of life, and cost of care.

TABLE 5

Desirable Product Characteristics

Rapid relief
Sustained duration of effect
Continuous topical application systems
Saliva stimulation, saliva enhancement
Pleasant, nonirritating: Texture, taste (taste variety available, mild), no sensitivity, stinging or burning (no alcohol, non-acidic pH), non-allergenic
Aseptic/no infection risk
No systemic adverse effects
Convenient: portability, packaging, storage
Cost considerations
Accessible
Compliance due to desirable qualities

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