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Xerostomia and Treatment Approaches: An Overview

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Abstract:
Xerostomia is a subjective sensation of dry mouth with objective evidence of decreased salivary flow. It is the most common, long-standing, multifactorial condition which increases the risk of oral diseases and affects 1–29% of the population, mostly women.It is observed in geriatric patients and in individuals using certain medications, those subjected to radiotherapy of the head and neck region or affected with autoimmune or systemic conditions. The main signs of xerostomia include dry mouth, problems with food ingestion and dryness of the oral mucosa and skin.So, these patients need special care for maintenance of oral and general health.Diagnosis of xerostomia is dependent upon a careful and detailed history and thorough oral examination. Management is multidisciplinary and multimodal: salivary stimulants, topical agents, saliva substitutes, and systemic sialogogues.

Keywords:*Saliva, Xerostomia, Dry Mouth, Salivary Substitutes, Sialogogues.*

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I. Introduction

Xerostomia is common oral concern for many patients.Xerostomia (dry mouth, mouth dryness, oral dryness) is dryness of oral cavity resulting from insufficient saliva secretion or a complete lack of saliva.Based on its pathogenesis, it is classified as:[a]True xerostomia– due to malfunction of the salivary glands, and [b]Pseudo xerostomia–subjectiveimpression of oral dryness despite normal secretory function of salivary gland.Xerostomia prevalence varies between 12% and 30% of the population and mostly women are affected[1,8].

Saliva plays a vital protective role in the oral cavity, and reduction in the quantity of saliva is known to increase the risk of oral diseases[2].Water is the main component of saliva, constituting 99% of its volume. The other components, comprising the remaining 1%, include inorganic salts of sodium, potassium, calcium and magnesium, and organic compounds, such as cholesterol, uric acid, immunoglobulins, enzymes and proteins. Normal secretion of saliva ranges from 0.25 to 0.35 mL/min, whereas the flow rate during sleep is 0.1 ml/min and during mastication, it increases to 4.0-5.0 ml/min.The principal functions of saliva include preparation of food for swallowing, modulation of taste, and initial digestion by salivary amylase and maltase. Other functions of saliva include moisturizing and dilution, both of which facilitate maintenance of mucosal integrity and has antibacterial property[3].

II. Etiology

The causes of xerostomia include multitude factors(Table 1) such as diseases of the salivary glands such as Sjögren's syndrome (SS), uncontrolled diabetes mellitus, radiation to the head and neck region, chemotherapy, and a number of commonly used medications. Injury to thehead or neck can damage the nerves thatare essential for the production and secretion of saliva by the salivary glands. Occasionally,xerostomia may besubjective, with no evidence of altered salivary flow and may be associated with psychological factors.

Drugs

Xerostomia is the most common adverse drug-related effect in the oral cavity. Till date, more than 500 medications have been reported causing xerostomia. The principal mechanism of drug-induced xerostomia is an anticholinergic or sympathomimetic action[4]. The risk for xerostomia increases with the number of drugs being taken and hence geriatric patients are more commonly affected[5]. Drugs causing xerostomia are given in Table 2.

Radiation therapy

Xerostomia is a common adverse effect of radiation therapy, when advised as primary, concomitant, or adjuvant treatment for head and neck tumors[5]. Salivary tissue is highly sensitive to radiation, with the parotid glands being most radiosensitive. The degree of xerostomia depends on the degree of exposure of salivary tissue

to the radiation and the radiation dose[6]. Treatment of oral carcinoma involves the administration of a dose of 60 Gy to 70 Gy, which can lead to a rapid decrease in salivary flow during the 1st week of radiation with an eventual reduction to 95% . By 5 weeks of radiation, the flow ceases and rarely recovers completely[2]. Radiation to a salivary tumor may avoid the contralateral gland and not cause severe xerostomia, while radiation to the nasopharynx may damage both the parotid glands, causing severe and permanent xerostomia. Irradiation with radioactive iodine used for treating thyroid disease may also cause salivary damage[4].

Table 1. Etiology of Xerostomia

Type of cause	Cause
Iatrogenic	Drugs Local radiation Radioiodine therapy (131I) Chemotherapy Chronic graft-versus-host disease
Developmental causes	Salivary gland agenesis / atresia
Pathologic causes	Sialolithiasis Sialadenitis
Diseases of salivary glands	Sjogren's syndrome Sarcoidosis
Metabolic disorders	Diabetes mellitus
Infections	HIV infection Hepatitis C virus infection
Other causes	Anxiety or Depression Psychological Mouth breathing Primary biliary cirrhosis Cystic fibrosis Amyloidosis Hemochromatosis Wegener's disease Triple A syndrome
Electrolyte loss	Dehydration Vomiting Diarrhea
Lifestyle factors	Smoking Excessive caffeine intake Alcohol abuse

Table 2. Drugs that may cause xerostomia

Anticholinergic agents • Atropine • Scopalamine *Antidepressants and antipsychotics* • Citalopram • Fluoxetine *Antihypertensive agents* • Captopril • Clonidine *Diuretic agents* • Chlorothiazide • Furosemide *Muscle relaxant agents* • Cyclobenzaprine • Orphenadrine *Sedative and anxiolytic agents* • Alprazolam • Triazolam *CNS analgesic agents* • Tramadol • Codeine	*NSAID and analgesic agents* • Naproxen • Ibuprofen *Antihistamines* • Diphenhydramine • Meclizine *Decongestant* • Pseudihepdrine *Bronchodilators* • Ipratopium • Albuterol *Antiemetics* • Meclizine • Bucilzine *Anticonvulsant* • Carbamazepine *Antiparkinsonian agents* • Carbidopa/ Levadopa *Miscellaneous* • Isotretinoin • Disopyramide • Tolterodine

Chemotherapy

Chemotherapy alone or in combination with radiation therapy is used to treat malignant tumors. Chemotherapeutic drug can make the saliva thick and causes dry mouth and is found to be the fourth most common symptom in advanced cancer patients undergoing chemotherapy[2].

Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic multisystem immune-mediated disorder characterized by inflammation of exocrine glands leading to dryness, particularly of the eyes and mouth. It can occur affecting only mouth and eye(primary SS), orin conjunction with other autoimmune rheumatic disease like rheumatoid arthritis or systemic lupus erythematosus (SLE) (secondary SS)[4]. A classic triad of symptoms is seen in Sjögren'ssyndrome which includexerostomia, dry eye syndrome/ keratoconjuntivitis sicca and polyarthritis.The xerostomia associated with primary and secondary Sjögren's syndrome has been attributed to the progressive lymphocytic infiltration that eventually destroys the secretory acini of the major and minor salivary glands[5].

Diabetes mellitus

Uncontrolled diabetic patients report polyuria and poor hydration which leads to reduced parotid flow rates in turn causing dry mouth than in those patients with well controlled diabetes mellitus. Xerostomia is one of the primary predisposing causes for oral candidiasis, median rhomboid glossitis, denture stomatitis, and angular chelitis with denture use in diabetic patients[2].

HIV disease

Salivary gland disease can affect 4% to 8% of adults and children with HIV infection. Salivary gland disease in HIV infection shows following principle clinical features: HIV salivary gland disease with associated xerostomia and salivary gland enlargement; Kaposi's sarcoma causing salivary gland enlargement; non-Hodgkin's lymphoma; intraglandularlymphadenopathy; and acute suppurativesialadenitis[4]. HIV salivary gland disease (HIV-SGD)affects up to 8% of adults (and may be more frequent in children) and is characterized by recurrent or persistent major salivary gland enlargement (most frequently parotid gland) and xerostomia. Salivary gland disease tends to arise in late HIV infection, but it can occasionally be the first manifestation of HIV disease.

Other causes of xerostomia

Epstein-Barr virus and human T-lymphotropic virus 1 have been implicated in xerostomia. Primary biliary cirrhosis, cystic fibrosis rarely cause xerostomia, as do salivary gland agenesis, with or without ectodermal dysplasia; triple-A syndrome; amyloidosis; and hemochromatosis[4].

III. Clinical Features Of Xerostomia

Xerostomia is unpleasant and, if prolonged, maylead to a reduced quality of life.Reduction in volume of saliva impairs both the immunological and non-immunological protective barrier; depending on the severity of xerostomia. Effects of long standing xerostomia are listed in Table 3.

Reduction of saliva may lead to dry mouth, soreness, or a sensation of a loss of or altered taste. Another manifestation may include an increased need to sip water when swallowing, difficulty with swallowing dry foods or an increasing aversion to dry foods[5].Xerostomia causes dysphagia,dysgeusia, dysarthria; bad breath, increased incidence of infections like oral thrush and ulcerations; fissures and cracked lips and tongue; burning sensation of lips tongue and oral mucosa (Burning Mouth Syndrome); milky saliva draining from the glandular ducts. Severe xerostomia can be associated with the development of cervical caries, resulting from the excessive accumulation of dental plaqueand calculus and candidal infection[1,2,4].

Table 3. Effects of long-standing xerostomia

• Increased frequency of caries, particularly cervical caries
• Proclivity toward acute gingivitis
• Accumulation of dental plaque and calculus leading to periodontal diseases
• Dysarthria, Dysphagia, Dysgeusia
• Frequent consumption of fluids during meals
• Bad breath, Oral mucosal soreness
• Burning of tongue and/or lips: Burning Mouth Syndrome (BMS)
• Depapillation of tongue , fissured and pebbled appearance of tongue
• Dry, sore, cracked lips
• Presence of "milky" saliva draining from the glandular ducts
• Proclivity toward candidal infection (eg, acute pseudomembranous candidiasis, median rhomboid glossitis, denture-associated stomatitis, angular cheilitis)

- Salivary gland enlargement (various causes)

IV. Diagnosis And Investigations

Diagnosis of xerostomia can be made by detailed patient's history, examination of the oral cavity, clinically by mouth mirror test and wafer test, radiologic, and laboratory-based test.Particular attention should be given to the reported symptoms, medication use, and past medical history[9].

The authors describe a simple method, a dental mirror test, for evaluation of oral mucosal friction as estimation of xerostomia[10]. Clinically, in mouth mirror test, back of the mouth mirror is drawn along the buccal mucosa and the friction is registered accordingly while wafer test is a semi-quantitative test in which the time taken for dissolution of wafer is noted in minutes and is recorded in grades to screen for xerostomia[11]. Clinical salivary gland hypofunction is indicated by dryness of the lips and buccal mucosa, absence of saliva production at the time of gland palpation, and increased DMFT score[2, 10].

After history recording and presence of these symptoms, standard sialometric tests are required. The simple, basic tests which evaluates the secretory function of the salivary glands include determination of stimulated salivary flow rate (s-SFR), unstimulated salivary flow rate (u-SFR), palatal secretion (PAL) and parotid secretion (PAR)[1]. Salivary gland imaging techniques like sialographyhelps to demonstrate ductal structures, detect salivary gland calculi and masses, and also find application in the identification of long-standing xerostomia.Salivary scintigraphy with technetium-99m (99mTc) helps in assessing salivary gland function. Ultrasonography demonstrates acinar and ductal structures. CT and MRI demonstrate parenchymal structure of the salivary gland tissue out of which MRI is preferred as it has better resolution for soft tissue. Other investigations like Schirmer's test and Rose Bengal staining can also be used. Biopsy of salivary glands helps in diagnosis of Sjogren's syndrome, HIV-associated salivary gland disease, sarcoidosis, amyloidosis, and in case of malignancy[2]. Evaluation of salivary function is listed in Table 4.

Table 4. Evaluation of salivary function

History

Focus on:

- Systemic or local diseases
- Trauma
- Medication list

Symptom questions

Predictive of hyposalivation (Fox et al., 1987)5

- "Do you sip liquids to aid in swallowing dry foods?"
- "Does your mouth feel dry when eating a meal?"
- "Do you have difficulties swallowing any foods?"
- "Does the amount of saliva in your mouth seem to be too little, too much, or you don'tnotice it?"

Physical examination

Extraoral examination

- Major salivary glands
- Lymph nodes

Intraoral examination

- Soft tissues
- Periodontium
- Dentition

Measurement of salivary output

- Unstimulated whole saliva flow
- Stimulated whole saliva flow
- Ductal flow of major salivary glands (e.g., parotid, submandibular/sublingual)

Sialochemical analyses

Serum laboratory studies

- Complete blood count with differential
- Autoimmune markers (e.g., antinuclear antibody, anti-SS-A, anti-SS-B, rheumatoid factor)
- Serum immunoglobulins
- Erythrocyte sedimentation rate

Investigation

- Schirmer's test
- Rose bengal staining

Salivary imaging

- Sialography

- Scintigraphy (99mTc)
- Ultrasonography
- Magnetic resonance imaging (MRI)
- Plain film
- Computed tomography (CT)

Salivary biopsy

- Labial minor salivary gland
- Fine-needle aspiration
- Major salivary gland

V. Management Of Xerostomia

After establishing a diagnosis, a step-wise management approach should be implemented.Identification of the underlying cause and education of the patient aimed at the implementation of systematic and proper oral hygiene, is a priority in the prevention and treatment of oral dryness. Avoidance of dry, acidic and salty foods as well as stimulants like tobacco and alcohol is recommended[1,2]. The principal aspects in management of long-standing xerostomia are given in Table 5.

Preventive measures

Preventive care should be administered in order to avoid oral complications due to xerostomia. It involves oral evaluation and examination every 4-6 months annually. To prevent dental caries due to hyposalivation, thorough maintenance of oral hygiene, a low-sugar diet, topical fluoride application, neutral pH sodium fluoride can be used. Fluorides and remineralizing solutions are available as varnishes, dentifrices, gels, and rinses, which can be used[2]. The practice of carrying and sipping bottled water throughout the day, also may offer relief for affected patients[5].

Table 5. Oral care aspects in patients with long–standing xerostomia

Oral hygiene

- Plaque control
- Oral hygiene instruction
- Dietary advice
- Chlorhexidine mouthwash or fluoride mouthwash daily (0.05%) to minimize the risk of caries.

Dentures

- Should fit well
- Implant-retained
- Provide instructions on denturehygiene.

Antifungals

- Nystatin pastilles
- Amphotericin lozenges
- Miconazole gel

Topical saliva substitutes

- Sugar-free gum and candies
- Oral moisturizers

Systemic therapies

- Pilocarpine
- Cevimeline, and others

Topical agents

Topical agents include chewing gums, saliva stimulants saliva substitutes which function in improving lubrication and hydration of oral tissues, maintaining oral health and function. Lubricating agents in the form of gels, aerosols, mouthwashes, lozenges, and toothpaste have been used for both subjective and objective improvement in the signs and symptoms of xerostomia[4].Saliva substitute preparations contain aqueous solutions like mucins, glycoproteins, salivary enzymes, and polymers such as carboxymethycellulosewhich protects soft tissues, or ions such as calcium, phosphates, or fluorides for protecting the hard structures of the teeth[2].

Sugar-free gum or sugar-free candies may help to increase salivary output and decrease oral mucosal friction, but they may be inconvenient and affect patients' compliance, and thus, frequent ingestion of sugar-free liquids may help[9]. Commercial mouth rinses that contain alcohol may desiccate the oral mucosa, and thus should be avoided by patients withxerostomia[5].Oral sprays, specifically oxygenated glycerol tri-ester, serve as an alternative treatment for dry mouth and are proven to be more effective thancommercially available salivasubstitutes. Recently, a mucin spray is found to be useful in elderly xerostomia patient undergoing radiation therapy. Salivary stimulant pastilles appear to be a useful adjuvant therapy for patients with dry mouth receiving oxybutynin chloride for detrusor instability[2]. Mucin-containing lozenges when compared to a placebo provided better effect[9]. One of the recent study of a topical oral moisturizer indicated significant subjective and

objective improvements in the signs and symptoms of xerostomia in individuals with SS and undergone radiation therapy. Standard bedside humidifiers and hyperthermic, supersaturated humidification have minimal benefit. An intraoral device containing saliva substitute and slowly release of the lubricant into the mouth is more acceptable to patients with xerostomia than has the use of the lubricant alone[4].

Milk helps in moistening and lubricating the oral mucosa, buffering oral acids, reducing enamel solubility, and contributes to enamel remineralization as it contains calcium, phosphate, and phosphoproteins that adsorb to enamel; hence, it is recommended as a salivary substitute.Pig products such as bovine/porcine and home remedies such as margarine and linseed oil are also used as salivary substitutes[2].

Systemic agents

Orally administered cholinergic agonists i.e. pilocarpine and cevimelinehave been successfully usedto increase salivary secretion.Pilocarpine is a parasympathetic agonist of acetylcholine muscarinic M3 receptors and has a potential benefit in limiting drug-induced xerostomia in patients using antihypertensive drugs and tricyclic antidepressants. Also recently, it has been discovered to have potential benefit in SS, especially where there is symptomatic extraoralexocrinopathy. The optimal dosage of pilocarpine is 5 mg given 4 times daily or 10 mg given thrice daily andshould be prescribed for at least 8 to 12 weeks[2, 4].Cevimeline is a salivary gland stimulant having stronger affinity for M3 muscarinic receptors and dosage of 30 mg thrice daily is used in the management of xerostomia secondary to irradiation, Sjogren's syndrome, HCV infection, and drug therapy[9].

Both pilocarpine and cevimelineshould be avoided for patients with respiratory disease (eg, asthma, chronic bronchitis, and chronic obstructive pulmonary disease) and those taking antihypertensive drugs because, although no notable drug interactions have been reported, interactions with β−blockers would seem possibleand also in patients with active gastric ulcers.Pilocarpine is also contraindicated in individuals with narrow-angle glaucoma and iritis[4]. Side effects include: excessive sweating, cutaneous vasodilatation, emesis, nausea, diarrhea, persistent hiccup, bronchoconstriction, hypotension, bradycardia, increased urinary frequency, and vision problems[6].

Bethanecol 25 mg thrice daily orally increases both the unstimulated and stimulated salivary flow rates in patients with xerostomia due to irradiation. Other drugs like carbacholine, anetholetrithione, and pyridostigmine are also useful. Bromhexine (32-48 mg daily) and zidovudine are found to increase salivary flow rates and limit xerostomia symptoms in Sjogren's syndrome patients. Antiretroviral therapy reduces salivary gland enlargement of HIV-related salivary gland disease[4]. Patients who were treated with psychotropic drugs(tricyclic antidepressants or neuroleptics) and experienced xerostomia benefited from yohimbine use which is an alpha 2 adrenoceptor antagonist[9].

Systemic corticosteroids may be of benefit in reducing the oral and ocular symptoms of Sjogren's syndrome. Corticosteroid irrigation (with prednisolone 2 mg/ml in normal saline) is clinically helpful by increasing the salivary flow rates in early stages of disease.Immunosuppressants like cyclosporine, cyclophosphamide, and thalidomide when administered systemically produce marked improvement in xerostomia[2].Chlorhexidine solution,nystatin/triamcinolone ointment is used for angular cheilitis and to treat candidiasis and clotrimazole troches: 10 mg dissolved orally 4–5 times daily for 10 days can be used.

Prosthodontic management

Patients with complete dentures who experience xerostomia are more likely to develop pain from denture irritation and loss of retention. The greater risk of developing candidiasis in edentulous patients may contribute to their discomfort. Dentures should be cleaned with chlorhexidine solution 0.2% overnight or chlorhexidine gel 1% two times a day. Soft denture liners or incorporation of metal in the palate of the maxillarydenture havebeen shown to be beneficial treatment options for some patients. Xerostomic patients wearing implant-supported dentures improved oral comfort and function when compared with conventional, mucosa-supported prosthesis users[5].

Salivary pacemakers

Neuroelectrostimulation increases salivary secretion, and thus the device salitron has been introduced. The first-generation stimulator has a probe which is applied intraorally to the mucosal surface for a few minutes daily which signals the neurons to induce salivation while second-generation salivary neuroelectrostimulator is a removable intraoral appliancewhich is similar to a mouthguard used to treat temporomandibular joint (TMJ) disorders and bruxism. Significant moistening of oral mucosal membrane and diminished xerostomia are reported during its application and 10 min after its removal[2, 3].

Psychological factors

Psychological factors causing xerostomia must be evaluated and treated. It is important to avoid irritants such as coffee, alcohol, or tobacco smoking. When at home, the patient can hold ice chips in his or her

mouth to provide moisture and possibly alleviate symptoms giving a placebo effect.Benzodiazepines such as ketazolam 15-30 mg at bed time, followed by gradual dose reduction are advised[2].

Acupuncture

Acupuncture is known to increase parasympathetic action, causing a release in neuropeptide and stimulating salivary flow and secretions, thereby reducing the incidence of xerostomia.The benefits of acupuncture regimen of 3 to 4 weekly treatments followed by monthly sessions were found to be successful[7].

Hyperbaric oxygen (HBO) therapy

HBO therapy can also be used in the treatment of xerostomia in radiation-induced cancer patients because of its angiogenetic and revascularization effects, but the exact mechanism is not clearly understood.Gerlach et al. conducted a study on the effect of HBO therapy in a series of 21 xerostomic patients with head and neck cancer at 1 and 2 years post administration of HBO and found aquantitative improvement in symptoms of xerostomia at 1 year post HBO therapy. Study Found reduced symptoms of xerostomia in patients who received HBO therapy within 1 year of radiation therapy than in those who received HBO 1 year after radiation therapy[12].

Tissue engineering

A combination of principles and methods of life sciences with those of engineering to develop materials and methods that can repair damaged and diseased tissue or to create entire tissue replacements is called tissue engineering.Ethically, there is a significant debate on tissue procurement.Artificial salivary gland is fabricated based on the principles of tissue engineering. The device consists of a blind-end tube fabricated from porous, slowly biodegradable substratum, coated with matrix components on the inner surface of the tube, in order to allow formation of polarized epithelial cell monolayer, providing unidirectional fluid secretion, and is surgically implanted in the buccal mucosa with an opening in the oral cavity, similar to the natural duct system[2].

VI. Conclusion

Xerostomia is a condition of dry mouth experienced by many patients. Its prevalence and negative effect on the patient's quality of life make it likely that the practitioner will encounter this condition on a regular basis. This concern along with increased risk of oral diseases in these patients has led the clinicians to diagnose, and provide preventive and definitive treatment to achieve oral comfort and function. Xerostomia results from the loss of saliva that may develop as a side effect from the use of medications, as a manifestation of Sjögren's syndrome secondary to a number of connective tissue diseases or as a complication of radiation therapy. At present, management of xerostomic patients is quite challengingand requires a multidisciplinary approach. So, a combination of various treatment modalities has become a better approach.

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