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Review Article

Xerostomia

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XEROSTOMIA

Xerostomia (dry mouth) is the subjective feeling of oral dryness. It is important to recognize that xerostomia is not a diagnosis, but a symptom with multiple possible causes.Although dry mouth is most frequently associated with altered salivary gland function, there are other etiologies for this oral issue. Xerostomia usually appears when resting unstimulated whole saliva flow rate is less than 0.1-0.2 mL/min and stimulated flow rate is less than 0.4 - 0.7 mL/min.

EPIDEMIOLOGY OF XEROSTOMIA

Xerostomia is a common oral concern for many patients. It is estimated that up to 10 percent of the general population experiences persistent oral dryness.Xerostomia is more frequent with increasing age, and over 25 percent of elders complain of daily dryness.3 However, it should be recognized that xerostomia is not a result of aging per se, and should not be dismissed as such. Salivary function in healthy, non-medicated elders does not vary significantly from younger individuals.

The presence of saliva is usually taken for granted, as it is not required for any life sustaining functions. Nevertheless its diminution or absence can cause significant morbidity and a reduction in patient's perceptions of quality of life. It is important to perform a complete evaluation of the patient with dry mouth, determining, if possible, the cause of the xerostomia so that appropriate management can be instituted in a timely manner.

PATHOPHYSIOLOGY

Daily salivary output is estimated to be approximately one liter per day, and flow rates can fluctuate by as much as 50 percent with diurnal rhythms. Salivary flow is categorized as unstimulated, or resting, and stimulated, as occurs when an exogenous factor is acting on the secretory mechanism. Both the parasympathetic and sympathetic nervous systems innervate the salivary glands. Parasympathetic stimulation induces more watery secretions, whereas the sympathetic system produces a sparser and more viscous flow. Therefore, a sensation of dryness may occur, during episodes of acute anxiety or stress, which cause changes in salivary composition owing to predominant sympathetic stimulation during such periods. Symptoms of a lack of saliva or oral dryness may be precipitated by dehydration of the oral mucosa, which occurs when output by the major/or minor salivary glands decrease and the layer of saliva that covers the oral mucosa is reduced.

Proposed mechanisms for hyposalivation include:

- Neurotransmitter receptor dysfunctions
- Salivary gland parenchymal destruction

- Immune dysregulation that may interfere with secretory processes
- Radiation-induced cellular DNA damage
- Alterations of fluid and electrolytes
- Combinations of the above

ETIOLOGY OF XEROSTOMIA

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

DRUGS

Xerostomia is the most common adverse drug-related effect in the oral cavity. To date, xerostomia has been associated with more than 500 medications. In addition, the synergistic effects of medications have been recognized and are increasingly common in patients taking multiple medications. Dry mouth is a common problem for many elderly persons.

The principal mechanism of drug-induced xerostomia is an anticholinergic or sympathomimetic action. Thus, the drugs most commonly implicated in xerostomia include tricyclic antidepressants, antipsychotics, benzodiazepines, atropinics, beta-blockers, and antihistamines. Therefore, xerostomia is common in patients treated for hypertension or mental illness. A wide range of other drugs can give rise to oral dryness. Some drugs – such as hydralazine, busulfan, quinidine sulfate, and thiabendazole – can give rise to primary Sjögren's syndrome-like disease; however, this clinical disease can be transient.The cause for which the drug is being taken may also be important. For example, patients with anxiety or depressive conditions may even report dry mouth in the absence of drug therapy.

RADIATION

Salivary gland tissue is highly vulnerable to radiation damage, with the parotid glands being most readily damaged. A radiation dose as low as 20 Gy can cause permanent cessation of salivary flow if given as a single dose. At doses above 52 Gy, salivary dysfunction is severe. Treatment of oral carcinoma conventionally involves the administration of a dose of 60 to 70 Gy, and this can lead to a rapid decrease in flow during the first week of radiation, with an eventual reduction of 95% in the region. By 5 weeks of radiation, the flow virtually ceases and rarely recovers completely. Both resting and stimulated salivary flow are inhibited. However, there is a compensatory hypertrophy of the unirradiated salivary gland tissue after a few months an up to a year, leading to some lessening in the sensation of oral dryness, but beyond this time, little further improvement occurs. The degree of xerostomia depends on the degree of exposure of the salivary tissue to the radiation, with partially irradiated glands having resultant higher flow rates than fully irradiated glands.

CHEMOTHERAPY

Various malignancies are treated with chemotherapy or a combination of radiation and chemotherapy. In a study of 127 patients with advanced cancer and xerostomia, xerostomia was found to be the most common symptom reported (78% of patients) and the degree of xerostomia was related to the total number of chemotherapeutic drugs used.[81] Xerostomia was ranked the third most distressing symptom. The severity of xerostomia was correlated with the severity of oral discomfort, dysgeusia, dysphagia, and dysphonia. Drugs used to treat cancer can make saliva thicker, causing the mouth to feel dry. Induction paclitaxel, carboplantin, and induction 5-fluoruracil followed by concurrent radiation and weekly paclitaxel/carboplantin in the treatment of locally advanced head and neck cancer can frequently cause xerostomia. Xerostomia was reported by 65% of 50 patients treated over 12 months with supradose selective intra-arterial cisplantin and concomitant standard radiation for inoperable stage IV head and neck squamous cell carcinoma. In vitro chemotherapeutic cytokines cause a pronounced inhibitory effect on the human salivary cell line.

LINICAL CONSEQUENCES OF XEROSTOMIA

The clinical consequences of long-standing xerostomia are:

- Increased frequency of caries (particularly cervical)
- Proclivity towards acute gingivitis
- Dysphagia
- Dysguesia
- Proclivity towards candidal infection (e.g. acute pseudomembranous candidiasis, median rhomboid glossitis, denture stomatis, angular cheilitis)
- Burning tongue/depapillation of tongue)
- Oral mucosal soreness
- Dry, sore, cracked lips
- Salivary gland enlargement (various causes)

a) Lipstick sign: In this test, the presence of lipstick or shed epithelial cells on the labial surfaces of the anterior maxillary teeth is indicative of reduced saliva (saliva would normally wet the mucosa and aid in cleansing the teeth).

b) Tongue bladesign: To test for this sign, the examiner holds a tongue blade against the mucosa; in a dry mouth, the tissue will adhere to the tongue blade as the blade is lifted away. Both

signs suggest that the mucosa is not sufficiently moisturized by the saliva.

ASSESSMENT OF XEROSTOMIA
SUBJECTIVE EVALUATION

1. VAS

A visual analog scale (VAS) is a line of, for example, 10mmon which the patient can mark the severity of the complaint. For Sjögren's syndrome, VAS scores are available for oral dryness, oral dryness during the day, oral dryness at night, difficulty swallowing dry food without any additional liquids, difficulty swallowing any food without any additional liquids, difficulty speaking without drinking liquids, and dry eyes (sensation of sand or gravel in the eyes).[93]

2. Dry mouth questionnaires

During the last decades, several questionnaires have been developed. A frequently used questionnaire in research projects on xerostomia is the Xerostomia Inventory. Eleven items of the Xerostomia Inventory are covering both experiential and behavioural aspects of xerostomia (Table). Scores to the 11 items are summated, providing a single score representing the subjective severity of xerostomia.

SIALOMETRY

Salivary gland function can be also measured objectively by measuring salivary flow rates. It has been estimated that a 50% reduction in salivary secretion needs to occur before xerostomia becomes apparent.97 Salivary output can be measured, and a collected amount of less than 0.12 to 0.16 mL/min (unstimulated) has been suggested to be the criteria for hypofunction.

INVESTIGATIONS OF PROLONGED XEROSTOMIA

The investigation of xerostomia centers upon a series of clinical, radiologic, and laboratory-based tests. The optimal approach to diagnosis is a systematic plan that first establishes the extent and cause of the complaint, then determines if salivary gland hypofunction is present and its severity, next establishes a definitive diagnosis, and finally assesses the potential of treatment. An initial evaluation should include a detailed evaluation of symptoms, a past and present medical history, a head/neck/oral examination, and an assessment of salivary function. On the basis of these and knowledge of the possible causes of xerostomia, certain specific investigations can be undertaken to confirm the working diagnosis which include:

- Hematological investigations like Hemoglobin gram%, MCV, WBC count, DLC, platelet count.
- Biochemical investigations like serum protein, alkaline phosphatase, liver transaminase, serum bicarbonate, serum potassium, ESR.
- Immunologic investigations like Rhematoid Factor, Anti nuclear antibodies, Anti-Scl 70, antibody to ds-DNA, Antibody to Ro and La antigens, antiphospholipid antibodies, cryglobulins, antimitochondrial antibodies, thyroid function tests.
- Salivary gland imaging like sialography, scintigraphy, ultrasononography, CT, MRI and Gallium scans.
- Histopathology of minor salivary gland tissue.
- Other investigational tools like Shirmer's test, Rose Bengal staining, Sialometry and sialochemistry.

MANAGEMENT OF LONG-STANDING XEROSTOMIA

1. **Preventive therapies:** e.g. supplemental fluoride, remineralizing solutions, optimal oral hygiene, non cariogenic diet.

- The use of topical fluorides in patients with salivary gland hypofunction is absolutely critical to control dental caries. The dosage chosen and frequency of application should be determined based on the severity of salivary dysfunction and the rate of caries development.
- It is also essential that patients maintain meticulous oral hygiene. Patients should be counseled as to diet, avoiding cariogenic foods and beverages and brushing immediately after meals.
- When salivary function is compromised, the normal process of tooth remineralization is compromised and demineralization is increased. Remineralizing solutions may be used to alleviate some of the effects of the loss of normal salivation.[96]
- Patients with dry mouth also experience an increase in oral infections, particularly mucosal candidiasis. The patient may present with redness of the mucosa and complaints of a burning sensation. Appropriated antifungal therapies should be instituted as necessary. E.g. antifungal pastilles or suspensions (nystatin) or gels (miconazole).

2. **Symptomatic treatment:** e.g. Water; oral rinses, gels, mouthwashes, increased humidification, minimize intake of caffeine and alcohol.

- Several symptomatic treatments are available. Water is by far the most important. Patients should be encouraged to sip water throughout the day; this will help moisten the oral cavity, hydrate the mucosa, and clear debris from the mouth.
- Use of sugar-free carbonated drinks is not recommended as the acidic content of many of these beverages is high and may increase tooth demineralization.
- An increase in environmental humidity is exceedingly important. The use of room humidifiers, particularly at night, may lessen discomfort markedly.
- There are a number of oral rinses, mouthwashes, and gels available for dry mouth patients.

- Patients should be cautioned to avoid products containing alcohol, sugar, or strong flavorings that may irritate sensitive mucosa.
- The frequent use of products containing aloe vera and vitamin E should be encouraged.
- Persistent cracking and erythema at corners of the mouth should be investigated for a fungal or bacterial cause.

There are many commercially available salivary substitutes.

Artificial saliva or saliva substitutes can be used to replace moisture and lubricate the mouth. These substitutes are available commercially, but they can also be compounded. Artificial salivas are formulated to mimic natural saliva, but they do not stimulate salivary gland production. Therefore, they must be considered as replacement therapy rather than a cure.Commercially available products come in a variety of formulations including solutions, sprays, gels and lozenges. In general, they contain an agent to increase viscosity, such as carboxymethylcellulose or hydroxyethylcellulose, minerals such as calcium and phosphate ions and fluoride, preservatives such as methyl- or propylparaben, and flavoring and related agents.

Some commercially available saliva substitutes include:

a. Wet Mouth: It is a gel containing sodium carboxymethyl cellulose (0.5%) and glycerine (30%)

b. Luborant: It is in the form of spray and contains sodium fluoride and sodium carboxymethyl cellulose.

c. Oral balance/Biotene: It is available as mouth rinse, lozenges and toothpaste. It contains several components such as polyglycerol methacrylate, lactoperoxidase and glucose oxidase.[99]

d. Saliva orthona (Nycomed): It is an oral spray containing porcine mucin. It is also available as a lozenge. However it is unsuitable for certain ethnic groups and vegetarians.

e. Saliva sure: It is a carboxymethylcellulose based substitute available in the form of lozenges.

f. Sensodyne Oasis Mouth Spray: Contains CMC and xanthan gum.

Most of these are only effective for less than an hour.An intraoral device containing saliva substitute which slowly releases the lubricant into the mouth has proved more acceptable to patients with xerostomia than has the use of the lubricant alone.

3. Local Salivary Stimulation: e.g. Sugar-free gums and candies

Chewing sucrose-free gums or mints is a convenient way to increase salivary flow. Gum chewing increases salivary flow through a combination of gustatory and mechanical stimulation. However, these actions are likely to be transient and the wearers of full dentures may be unable to use them. A combination of a mouthwash, toothpaste, and chewing gum in one study improved many of the symptoms of radiation-induced xerostomia, and another study indicated that chewing gum may be more effective than artificial saliva in the management of xerostomia. It has been shown that on chewing flavored gum, the salivary flow rate increases initially but declines as the flavor is lost from the gum, and as the gum softens with chewing. E.g. **Salix*** is a buffered citric acid tablet which can be sucked 3-4times/day.

4. Systemic salivary stimulation: e.g. Parasympathomimetic secretogogues.

The use of systemic secretagogues for salivary stimulation has long been examined. More than 24 agents have been proposed as a means of stimulating salivary output systemically. These include:

Cholinergic agonists. Orally administered agonists of the muscarinic M3 receptor (pilocarpine and cevimeline) have been approved by the US Food and Drug Administration to increase salivary secretion.

Pilocarpine: Pilocarpine is a parasympathetic agonist of acetylcholine muscarinic M3 receptors and thus stimulates secretion by exocrine glands such as the salivary, sweat, lacrimal, and respiratory mucous glands; the contraction of smooth muscle;and the motility of the gastrointestinal and urinarytracts, gall bladder, biliary ducts, and bronchi. These latter effects have dissuaded some clinicians to use pilocarpine. It is available as **Salagen*** (pilocarpine hydrochloride) 5 mg tablets.

Cevimeline. Therapy with cevimeline, 30 mg 3 times daily, seems to be well tolerated and provides substantive relief of xerostomia symptoms.[110] It has been suggested that cevimeline may have clinical application in the management of xerostomia secondary to irradiation, SS, HCV infection, and drug therapy.Clinical trials have shown it to be more effective than placebo in relieving symptoms of dry mouth.

Bethanechol: Bethanechol, which has both muscarinic and nicotinic agonist actions, was suggested to be of potential use in the management of drug-induced xerostomia. Bethanechol (25 mg, 3 times daily orally) was found to increase the unstimulated and stimulated salivary flow rates of patients with xerostomia secondary to radiation, but objective changes in salivary flow rates did not always correlate with symptomatic improvement. However, adverse effects, which may include nausea and diarrhea, are infrequent.

Carbacholine: It has been suggested that carbacholine may be of benefit in the treatment of radiation induced xerostomia.

Pyridostigmine: Pyridostigmine is a cholinesterase inhibitor with both nicotinic and muscarinic agonistic action. Available data, including those from a placebo-controlled study, suggest that pyridostigmine may be of benefit in the treatment of drug-related xerostomia, but there are no data on the efficacy of

this agent in the management of other common disorders giving rise to xerostomia.

Bromhexine: Bromhexine (32-48 mg daily) may increase salivary and lacrimal flow in patients with SS.

OTHER METHODS OF STIMULATING SALIVATION

Electrostimulation: It has been suggested that electrostimulation may increase salivary flow in some patients with SS, and one study has shown an improvement in xerostomia symptoms in a group of persons with SS who were treated with electrostimulation.

Acupuncture: The results of studies of patients with radiation-induced xerostomia, but not SS, have suggested that acupuncture may cause a sustainable increase in the salivary flow rates. One report has suggested that acupuncture may provide some symptomatic improvement in some patients requiring palliative care, and another more-recent study demonstrated the benefits of a regimen of 3 to 4 weekly treatments followed by monthly sessions.

Dietary supplementation: The results of 1 placebo-controlled investigation suggested that a herbally based agent with vitamin supplements (LongoVital, LV, Denmark) cause a prolonged increase in unstimulated salivary flow and a reduction in rose bengal dye scores in a group of patients with SS. It has been suggested that evening primrose oil, rich in fatty acids and important in inhibiting prostaglandins, may enhance salivary flow in some individuals with SS. It has also been suggested that those with drug-induced xerostomia may benefit from chewing cappuccino coffee, yet only temporary improvement is provided for xerostomia. Positive effects on symptoms in patients with SS were seen after the use of linseed extract**(Salinum)** with or without chlorhexidine.

OTHER SYSTEMIC THERAPIES

Highly active antiretroviral therapy may reduce the salivary gland enlargement of HIV-related salivary gland disease. A recent study has suggested that **anhydrous crystalline maltose** may cause adjective and symptomatic improvement in both xerostomia and xerophthalmia. **Ambroxol (Mucosolvan)** 135 mg daily for 8 weeks was shown in another study to improve sicca symptoms in those with SS. Sustained improvement of active primary SS may be possible with **infliximab** treatment.

SUMMARY OF ORAL CARE IN PATIENTS WITH XEROSTOMIA

- **Oral hygiene:** Plaque control, oral hygiene instruction, dietary advice, chlorhexidine mouthwash or fluoride mouthwash daily to minimize the risk of caries
- **Treatment of underlying systemic disorders**
- **Antifungal therapy:** Nystatin pastilles, amphotericin lozenges, miconazole gel
- **Topical saliva substitutes**
- **Sugar-free gum and candies; oral moisturizers**
- **Systemic therapies: Pilocarpine, cevimeline, and others**

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