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Review Article

Salivary Pacemakers: A review

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ABSTRACT

Xerostomia is the medical term for the subjective complaint of dry mouth due to a lack of saliva. Xerostomia is sometimes colloquially called pasties, cottonmouth, drooth, doughmouth or des (like a desert). Several diseases, treatments and medications can cause xerostomia. It is also common in smokers. Treatment of xerostomia is a common clinical challenge in the oral medicine practice. Although some treatments have been used to improve the symptoms of xerostomia, none is completely satisfactory for the patients who suffer of this alteration. This review is aimed at presenting new developments for the treatment of xerostomia.

Key Words: Electrostimulation, hyposalivation, saliva, xerostomia

INTRODUCTION

Xerostomia is a symptom of oral dryness that occurs when salivary flow is not sufficient to compensate the fluid loss from the oral cavity. In the majority of cases, it results from loss of salivary gland hypofunction.[1] Xerostomia is a common problem. Its prevalence in the general population has been estimated to be 10-29%, women being more commonly affected than men.[2] Although more likely in middle to late life (perhaps reflecting the anticholinergic action of many drugs), xerostomia can affect young adults, but rarely children.[3,4]

The presence of saliva is usually taken for granted, and it is not required for any life-sustaining functions. Never the less, its diminution or absence can cause significant morbidity and a reduction in a patient's perceptions of quality of life.[5,6] The primary constituents of saliva are water, proteins and electrolytes.[7] These components enhance taste, speech and swallowing, and facilitate irrigation, lubrication and protection of the mucous membranes in the upper digestive tract.[5] Additional physiological functions of saliva provide antimicrobial and buffering activities that protect the teeth from dental caries.[7]

Upon meeting the dry mouth patients, dentists face a problem difficult to treat. Treatment with lubricants or salivary substitutes and salivary stimulation by gustatory or masticatory methods may generate an improvement, but xerostomia recurs once the treatment is interrupted.[8] Pharmacological agents, like pilocarpine HCl, have been studied extensively; nevertheless, more than one-third of the patients display adverse effects similar to those produced by other cholinergic drugs, including gastric upset, perspiration, Tachycardia, Bradycardia, Arrhythmia, increases of pulmonary secretions, muscular tone and urinary frequency and blurred vision.[9,10] In a recent study, individuals with xerostomia expressed their wish of a functional non-pharmacological method for their treatment; however, none of the presently available treatments fulfills these expectations.[11]

The objective of this review is to present the advances of neuroelectrostimulation for the treatment of xerostomia, based on the accumulated knowledge of neurological control of salivary secretion.

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ETIOLOGY

Hyposalivation may occur with use of medications, as complications of connective tissue and autoimmune diseases, with radiation therapy to head and neck or with a number of other conditions.

Hyposalivation contributes to a number of health problems. It can produce serious negative effects on the patients' quality of life by affecting dietary habits, nutritional status, speech, taste and tolerance to dental prosthesis and increasing the risk of oral infection, including candidiasis, susceptibility to dental caries, periodontal disease and tooth loss.[12]

DRUGS ASSOCIATED WITH XEROSTOMIA*[5]

Category	Generic name
Anticholinergic agents	Atropine
	Belladonna
	Benztropine
	Oxybutynin
	Scopolamine
	Trihexyphenidyl
Antidepressant and antipsychotic agents	
Selective serotonin-reuptake inhibitors	Citalopram
	Fluoxetine
	Paroxetine
	Sertraline
	Venlafaxine
Tricyclic antidepressants	Amitriptyline
	Desipramine
Heterocyclic antidepressants	Imipramine
	Haloperidol
	Mirtazapine
Monoamine oxidase inhibitors	Pimozide
Atypical antidepressants	Phenelzine
	Bupropion
	Nefazodone
	Olanzapine
Diuretic agents	Chlorothiazide
	Furosemide
	Hydrochlorothiazide
	Triamterene
Antihypertensive agents	Captopril
	Clonidine
	Enalapril
	Guanfacine
	Lisinopril
	Methyldopa
Sedative and anxiolytic agents	Alprazolam
	Diazepam
	Flurazepam
	Temazepam
	Triazolam
Muscle relaxant agents	Cyclobenzaprine
	Orphenadrine
	Tizanidine
Analgesic agents	
Central nervous system/opioids	Codeine
	Meperidine
	Methadone
	Pentazocine
	Propoxyphene
	Tramadol
Non-steroidal anti-inflammatory agents	Diflunisal
	Ibuprofen
	Naproxen
	Piroxicam
Antihistamines	Astemizole
	Brompheniramine
	Chlorpheniramine
	Diphenhydramine
	Loratadine
	Meclizine

*Drugs listed have been reported to have a xerostomia incidence of 10% or more

SALIVARY GLANDS

The parotid gland is, histologically, a serous type of gland and secretes 20% of the total saliva. The submandibular salivary gland is, histologically, a mixed type of gland and secretes 70% of the total saliva. The sublingual salivary gland is, histologically, a mixed type of gland and secretes 5% of the total saliva. In salivary glands, secretory granules containing salivary enzymes are discharged from the acinar cells to the ducts. About 1500 mL of saliva is secreted per day.[13]

NEUROLOGICAL CONTROL OF SALIVARY SECRETION

Salivary gland secretion is regulated by the autonomic nervous system. Acetylcholine agonists act on the parasympathetic and muscarinic receptors of those exocrine glands, inducing high electrolyte containing salivary secretion, whereas sympathetic stimulation produces the protein component of the saliva. Thus, parasympathetic stimulation generates abundant saliva with low protein concentration and sympathetic stimulation produces little saliva with high protein concentration and viscosity.[14]

Physiologically, salivary secretion is regulated by a three-component reflex arch, including (a) afferent receptors and nerves that carry impulses created by taste and mastication activities, (b) a central

connection and processing nucleus (salivation center) and (c) an efferent reflex arm constituted by parasympathetic and sympathetic nerves bundles that separately, but in coordination, innervate the salivary gland blood vessels and acini. The afferent nerves carry impulses from the periphery to the salivation center in the medulla oblongata, which in turn directs signals to the efferent part of the reflex arch leading to salivation.[14,15]

The assessment of severity of xerostomia is done by subjective and objective techniques. The visual analogue scale, Zimmerman xerostomia questionnaire and late effect of normal tissues subjective objective management analysis (LENT SOMA) scale are some of the methods to find and grade the severity of xerostomia. The salivary gland secretory ratio (SGSR), determined by dynamic salivary 99mTcscintigraphy, is an objective measure of salivary gland function.[16,17]

Rydholm and associates conducted a study to explore the global effects of xerostomia, with a specific focus on the psychological and social consequences. Four main categories were identified in the study:[18]

1. Subjective discomfort: e.g. dryness or burning sensation.
2. Loss of function: e.g. articulation or swallowing.
3. Increased infection: e.g. oral thrush and ulcerations.
4. Psychological effects: Including shame, increased feelings of being a patient rather than a person and tendency to avoid social contact resulting in loneliness.

Xerostomia and associated symptoms have a considerable negative global impact, resulting in shame, anxiety, disappointments and verbal communication difficulties. They should therefore focus more on the management of xerostomia, which is often neglected in the palliative care.[19]

Individuals with xerostomia often wish for a functional and non-pharmacological ("natural") cure. There thus remains a need for a treatment of xerostomia that is effective, convenient and safe.[11]

More recently, the use of extraoral transcutaneous electric nerve stimulation (TENS) over the parotid gland was reported to increase saliva production in healthy individuals and patients with radiation-induced xerostomia, suggesting that TENS might directly stimulate the auriculotemporal nerve (efferent pathway) that supplies the secretomotor drive to the parotid gland.[20,21]

SALIVARY PACEMAKERS

First-generation electrostimulating devices

Neuroelectrostimulation to increase salivary secretion led to production of a device that was marketed in the USA (Salitron). The probe was applied to the intraoral mucosal surfaces by the user (between the dorsum of the tongue and the palate) for a few minutes each day and delivered a stimulating signal to sensitive neurons of the mouth to induce salivation [Figure 1].[22-24] Using this some what clumsy apparatus, it was found that such neuroelectrostimulation, when delivered repeatedly, led to an immediate (direct) response (increase of salivation as a result of the stimulation) and a cumulative long-term (indirect) response (sustained increase of basal salivary flow rate) as well as subjective improvement in symptomatic xerostomia. The device gave promising results in proof-of-principle clinical studies and did not give rise to any concomitant local or systemic adverse effects. However, its wider use was hampered by its large size, high price and lack of user-friendliness. To circumvent some of the limitations of this first-generation device, a European Commission-funded research consortium developed novel miniature intraoral neuro-electrostimulators to enhance salivary flow (Saliwell project). Two devices were produced, one designed to be part of a removable intraoral splint appliance (second-generation device) and the other to be fixed to an osteointegrated dental implant (third-generation device).

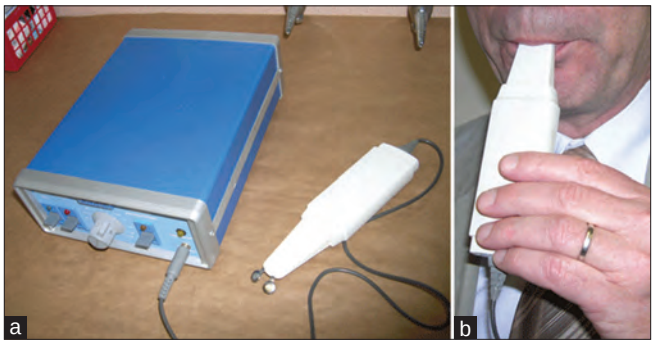

Figure 1: (a)First-generation neuroelectrostimulation device consisted of a hand-held probe, tipped with stainless steel electrodes, and a console that housed a battery and the electronic signal-generating power source, the size and shape of which were similar to a video or CD player. (b)The probe was applied to the intra-oral mucosal surfaces by the user (between the dorsum of the tongue and palate) for a few minutes each day and delivered a stimulating signal to sensitive neurons of the mouth to induce salivation

Second-generation devices

The second-generation salivary neuroelectrostimulator (GenNarino Saliwell Ltd. Germany) is a removable intraoral appliance produced for individual patients by using their teeth pattern molds. It is similar to a mouth guard used to treat temporomandibular joint disorders and bruxism. It has a horseshoe-like shape and fits on the lower dentition [Figure 2]. It is designed so that it is easy to insert and remove by the patient him- or herself. The electronic components are embedded within the appliance to allow safe and contamination-free intraoral application. A remote control permits the patient to communicate with the device and modify its functions [Figure 2].

The results of the study demonstrated that the device was relatively well tolerated by all patients and did not, with the exclusion criteria applied, give rise to any local or systemic adverse effect. Significant moistening of the oral mucosal membranes was recorded objectively ($P < 0.0001$), and diminished xerostomia was reported subjectively ($P < 0.005$).[25] The device was effective in reducing dryness of the mouth during application and up to 10 min after its removal.

Figure 2: Second-generation removable device consists of three components: A miniaturized electronic stimulator that has a signal generator, power source and conducting circuitry; an intraoral removable appliance; and an infrared remote control. The miniaturized electronic stimulator is mounted in a removable intraoral appliance (a); which is under remote control that activates the stimulator (b); This device is applied into the mouth in a non-invasive manner (c)

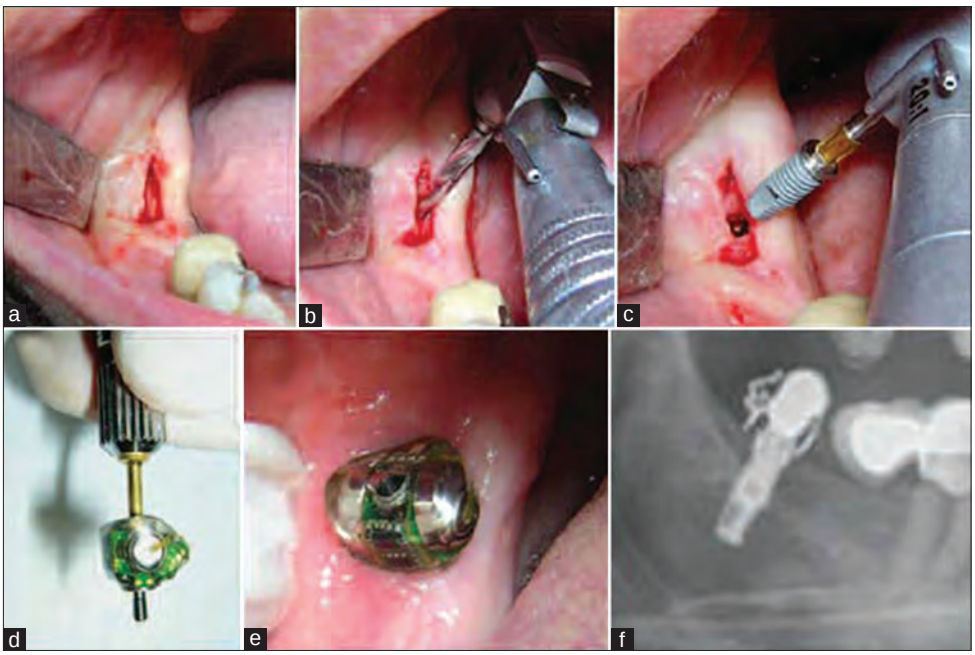

Figure 3: Third-generation implant-supported neuroelectrostimulating device can be permanently applied into the oral cavity as it can be screwed onto an osteo-integrated dental implant inserted in the third molar area. Figure shows the implantation procedure and application of the device. Transmucosal exposure of mandibular bone (a) is followed by preparation of the implant bed in mandibular bone (b) and insertion of the dental root implant (c) The neuroelectrostimulating device is shown in its applicator (d) and mounted onto the root implant (e) Radiograph of the implant-supported device (f)

Dental implant-based third-generation intraoral device

Some patients may require frequent and/or constant stimulation of the salivary glands. Therefore, a miniature neuroelectrostimulating device to be permanently implanted into the oral cavity was developed (the Saliwell Crown Saliwell Ltd. Germany) [Figure 3]. Use of this dental implant-based neuroelectrostimulator avoids the inconvenience associated with the repeated application and removal of a splint-based stimulator. The components of the second-generation device were miniaturized and packaged into a device that has the dimensions and shape of a molar tooth. This device can be mounted on a commercially available osteointegrated implant. A wetness sensor has been embedded into the device to detect changes in wetness/dryness.

This third-generation implantable device has been developed not only (1) to generate continuous or frequent stimuli, (2) to be applied into the oral cavity without interfering with regular oral functions and (3) to sense the wetness/dryness status of the oral cavity and automatically increase/decrease the stimulus within a preset range (autoregulatory mode) but also (4) to be controlled by the patient via a remote control.

The osteointegrated implant is positioned in the region of the lower third molar (wisdom tooth) to ensure close proximity to the lingual nerve that carries both afferent and efferent salivary impulses and to avoid interference with normal oral function. The necessary surgery is relatively straight forward, and the posterior location of the device ensures that there are no aesthetic concerns [Figure 3].

A clinical trial to investigate the long-term effect of this third-generation neuroelectrostimulatoron salivary function and symptoms of xerostomia is currently under way, and if the results are promising, it would be expected that this could become the most convenient and safe means to treat xerostomia.[11]

CONCLUSION

Xerostomia is the main clinical effect that interferes with nutrition and use of dentures, deteriorates oral hygiene and predisposes patients to oral candidiasis and dental problems (e.g. dental caries). Xerostomia and its associated symptoms have a considerable, negative global impact, resulting in shame, anxiety, disappointments and verbal communication difficulties. Hyposalivation and xerostomia have multiple causes, but almost all of them, regardless of their etiology, affect in particular the resting (moisturizing) salivary flow. Neuroelectrostimulation of salivary glands takes the still remaining salivation reserves into therapeutic use. For patients with hyposalivation and xerostomia-related impaired quality of life and those who require long-term therapy, the second-and third-generation intraoral neuroelectrostimulating devices may offer a new non-medicinal means of treatment. Preliminary results showing increased salivary secretion and progressive improvement of xerostomia symptoms are demonstrating the effectiveness of these intraoral devices. The prevention and treatment of xerostomia should be the primary concern and coordinated effort of a radiation oncologist and a dental surgeon now-a-days.

REFERENCES

1. Fox PC, van der Ven PF, Sonies BC, Weiffenbach JM, Baum BJ. Xerostomia: Evaluation of symptom with increasing significance. J Am Dent Assoc 1985;110:519-25.
2. Porter SR, Scully C, Hegarty AM. An update of the etiology and management of xerostomia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:28-46.
3. Billings RJ, Proskin HM, Moss ME. Xerostomia and associated factors in a community-dwelling adult population. Community Dent Oral Epidemiol 1996;24:312-6.
4. Schein OD, Hochberg MC, Muñoz B, Tielsch JM, Bandeen-Roche K, Provost T, *et al.* Dry eye and dry mouth in the elderly: A population-based assessment. Arch Intern Med 1999;159:1359-63.
5. Guggenheimer J, Moore PA. Xerostomia: Etiology, recognition and treatment. J Am Dent Assoc 2003;134:61-9.
6. Sreebny LM, Valdini A. Xerostomia. A neglected symptom. Arch Intern Med 1987;147:1333-7.
7. International Dental Federation. Saliva: Its role in health and disease. Working Group 10 of the Commission on Oral Health, Research and Epidemiology (CORE). Int Dent J 1992;42(Suppl2):287-304.
8. Greenspan D. Xerostomia: Diagnosis and management. Oncology (Williston Park) 1996;10:7-11.
9. Grisius MM. Salivary gland dysfunction: A review systemic therapies. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:156-62.
10. Guijaaro Guijarro B, López Sánchez AF, Hernández Vallejo G. Treatment of xerostomia: A review. Med Oral 2001;6:7-18.
11. Lafaurie G, Fedele S, Lopez RM, Wolff A, Strietzel F, Porter SR, *et al.* Biotechnological advances in neuro-electro-stimulation for the treatment of hyposalivation and xerostomia. Med Oral Pathol Oral Cir Bucal 2009;14:E76-80.
12. Atkinson JC, Wu AJ. Salivary gland dysfunction: Causes, symptoms, treatment. J Am Dent Assoc 1994;125:409-16.
13. Ganong WF. Regulation of gastrointestinal function. In: Ganong WF, editor. Review of Medical Physiology. 7th ed.

Connecticut: Appleton and Lange; 1995. p. 260-72.
14. Proctor GB, Carpenter GH. Regulation of salivary gland function by autonomic nerves. Auton Neurosci 2007;133:3-18.
15. Pederson AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. Oral Dis 2002;8:117-29.
16. Zimmerman RP, Mark RJ, Tran LM, Juillard GF. Concomitant pilocarpine during head and neck irradiation is associated with decreased posttreatment xerostomia. Int J Radiat Oncol Biol Phys 1997;37:571-5.
17. Haddad P, Karimi M. A randomized, double-blind placebo-controlled trial of concomitant pilocarpine with head and neck irradiation for prevention of radiation-induced xerostomia. Radiother Oncol 2002;64:29-32.
18. Rydholm M, Strang P. Physical and psychosocial impact of xerostomia in palliative cancer care: A qualitative interview study. Int J Palliat Nurs 2002;8:318-23.
19. Atri R, Dhankhar R, Nair V, Kaushal V. Management of radiation induced xerostomia in head neck cancer patients. J Oral Health Comm Dent 2007;1:33-9.
20. Wong RK, Jones GW, Sagar SM, Babjak AF, Whelan T. A phase I-II study in the use of acupuncture-like transcutaneous nerve stimulation in the treatment of radiation-induced xerostomia in head-and-neck cancer patients treated with radical radiotherapy. Int J Radiat Oncol Biol Phys 2003;57:472-80.
21. Hargitai IA, Sherman RG, Strother JM. The effects of electrostimulation on parotid saliva flow: A pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:316-20.
22. Steller M, Chou L, Daniels TE. Electrical stimulation of salivary flow on patients with Sjögren's syndrome. J Dent Res 1988;67:1334-7.
23. Talal N, Quinn JH, Daniels TE. The clinical effects of electrostimulation on salivary function of Sjögren's syndrome patients. A placebo controlled study. Rheumatol Int 1992;12:43-5.
24. Weiss WWJr, Brenman HS, Katz P, Bennett JA. Use of an electronic stimulator for the treatment of dry mouth. J Oral Maxillofac Surg 1986;44:845-50.
25. Strietzel FP, Martín-Granizo R, Fedele S, Lo Russo L, Mignogna M, Reichart PA, *et al.* Electrostimulating device in the management of xerostomia. Oral Dis 2007;13:206-13.

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