Salivary pacemakers – Revealing the incognito.

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Abstract
The treatment of xerostomia has been a challenge for the medical and dental practitioners over the ages. The present treatment modalities have not been able to provide satisfactory results for a long-term period. The invention of SALIVARY PACEMAKERS is a problem-solving boon. The salivary pacemakers and their current advancements have improved the prognosis of xerostomia. Recently, the third-generation pacemakers (dental implant based salivary pacemakers) have been able to provide a single fold treatment option for both edentulism and xerostomia. This review provides an insight into etiology of xerostomia and focuses on the treatment of the same via salivary pacemakers.

Keywords: Salivary pacemakers, xerostomia, neuro-electro stimulation**.**

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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 or in cases where there is a reduced function or hypofunction of the salivary gland.[1] Xerostomia is a problem that is frequently seen in the population. The prevalence of xerostomia has been estimated to be 10-29%, among the general population with a predilection for women more common than men.[2] The condition usually affects persons in the middle age to late life mainly due to the anticholinergic action of many drugs, however young adults can also suffer from xerostomia, but rarely children.[3,4]

Still today, very less importance is given to saliva, it's presence and the major functions that saliva has, and it is a very wrong notion that saliva 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 major components of saliva are water, proteins and electrolytes.[7] Some of the important functions of saliva include enhancing taste, speech and swallowing by helping in the formation of bolus and facilitate irrigation, lubrication and protection of the mucous membranes in the upper digestive tract.[5] Additional physiological functions of saliva provide antimicrobial, digestive actions due to the presence of salivary amylase, lipase etc. and buffering activities due to the presence of sodium bicarbonate that protect the teeth from dental caries.[7]

Dental Surgeons face a problem difficult to treat in patients suffering from der mouth. Treatment with lubricants or salivary substitutes and salivary stimulation by gustatory or masticatory methods is beneficial, but once the treatment is interrupted, a relapse of the condition is seen.[8] Extensive studies have been done on pharmacological agents, like pilocarpine HCl, but adverse effects have been observed in more than one-third of the patients similar to those produced by other cholinergic drugs. Gastric upset, perspiration, tachycardia, bradycardia, arrhythmia, increases of pulmonary secretions, muscular tone and

urinary frequency and blurred vision are some of the noted adverse effects.[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 primary goal of this review is to present the advances of neuro-electrostimulation for the treatment of xerostomia, based on the scaffold of neurological control of salivary secretion.

Etiology

Hyposalivation may occur with use of medications (Table 1), as complications of connective tissue and autoimmune diseases, with radiation therapy to head and neck or with a number of other conditions.

Hyposalivation leads to a number of health problems. Some examples include serious negative effects on the patients' quality of life by modifying 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]

Salivary Glands

The parotid gland - histologically, a serous type of gland, secretes 20% of the total saliva. The submandibular salivary gland - histologically, a mixed type of gland, secretes 70% of the total saliva. The sublingual salivary gland - histologically, a mixed type of gland, secretes 5% of the total saliva. Secretory granules in the salivary glands contain salivary enzymes. Stimulation of these granules causes discharge of salivary enzymes 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 (Figure 1). Action of the acetylcholine agonists on the parasympathetic and muscarinic receptors of those exocrine glands, causes release of high electrolyte containing salivary secretion, whereas sympathetic stimulation produces the saliva rich in protein. Thus, parasympathetic stimulation generates abundant saliva with low protein concentration and sympathetic stimulation produces little saliva with high protein concentration and viscosity.[14]

The secretion of saliva is regulated by a three-component reflex arch, components of which are:

(a) afferent receptors and nerves that carry impulses created by taste and mastication activities.

(b) a central connection and processing nucleus (salivation center)

(c) an efferent reflex arm composed of parasympathetic and sympathetic nerves bundles that function differently, but in coordination, and 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]

Clinical 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 determine and grade the severity of xerostomia. An objective measure of salivary gland function is the salivary gland secretory ratio (**SGSR**), determined by dynamic salivary 99mTcscintigraphy.[16,17] A study conducted by Rydholm and associates to explore the global effects of xerostomia, emphasized mainly on the psychological and

social consequences. Four main categories were noted 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, implications of which are shame, anxiety, disappointments and verbal communication difficulties. The management of xerostomia should be the area of primary importance, which is often neglected in the palliative care.[19]

Patients suffering from xerostomia frequently desire for a functional and **non-pharmacological** ("natural") cure. Keeping this aspect in mind, there is a need for a treatment of xerostomia that is effective, convenient and safe. [11]

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

Neuro-Electric Stimulation of The Salivary Glands (Figure 2).

Salivary Pacemakers

First-generation electro stimulating devices

The concept of neuro-electrostimulation to increase salivary secretion led to production of a device that was marketed in the USA (Salitron). In this the probe was applied in between the dorsum of the tongue & palate to the intraoral mucosal surfaces by the applicator and kept in position for a few minutes before removing each day. This resulted in delivery of a stimulating signal to sensitive neurons of the mouth to induce salivation (Figure 3). [22,23,24] With this, a bit of an inelegant machinery, it was concluded that such neuro-electrostimulation, when delivered repeatedly has some beneficial response. Electro stimulation led to an immediate (direct) response by causing an increase of salivation as a result of the stimulation and a cumulative long-term response, also referred to as indirect response (sustained increase of basal salivary flow rate) as well as resulted in a subjective improvement in symptomatic xerostomia. Promising results were seen in clinical studies with this device and did not give rise to any local or systemic adverse effects.

Disadvantages

a. Large size of the apparatus reduced its popularity
b. High Price
c. Not user friendly

In an effort to overcome the shortcomings of this first-generation device, a European Commission-funded research consortium developed novel miniature intraoral neuro-electro stimulators to increase salivary flow (Saliwell project). Two devices were produced, one comprised of a removable intraoral splint appliance (**second-generation device**) and the other to be fixed to an Osseo integrated dental implant (**third-generation device**).

Second-generation devices

The second-generation salivary neuro-electro stimulator (GenNarino Saliwell Ltd. Germany) is a removable intraoral appliance customized for individual patients by using the teeth pattern molds of the patients. It is more-or-less similar in design to a mouth

guard used for the treatment of temporomandibular joint disorders and bruxism. The device is horseshoe shaped and fits on the lower dentition (Figure 4). The design is such that it is easy to insert and remove by the patient him-or herself. The electronic components are situated within the appliance which allows for a safe and contamination-free intraoral application. The device is supplemented with a remote control which permits the patient to communicate with the device and alter its functions (Figure 4). 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.

(a)The miniaturized electronic stimulator is mounted in a removable intraoral appliance

(b) remote control which activates the stimulator

(c) The device is positioned into the mouth in a non-invasive manner

A study was conducted to analyze the efficacy of the second-generation devices. The results of the study concluded that the device was relatively well tolerated by all patients and did not, give rise to any local or systemic adverse effect applying the exclusion criteria of the research. Significant moistening of the oral mucosal membranes was recorded objectively ($P < 0.0001$), and diminished xerostomia was reported subjectively ($P < 0.005$). [25] The Conclusion drawn from the study was that the device was effective in reducing dryness of the mouth (Xerostomia) during application and up to 10 min after its removal.

Dental implant-based third-generation intraoral device

There is a requirement of frequent and/or constant stimulation of the salivary glands to promote salivation in some patient who suffer from severe grades of xerostomia. This led to the discovery of a miniature neuro-electro stimulating device that can be permanently implanted into the oral cavity with continuous stimulation of the salivary glands without the need of removing the device from the mouth. One such was developed (the Saliwell Crown Saliwell Ltd. Germany) (Figure 5). Use of this dental implant-based neuro-electrostimulator avoids the inconvenience associated with the repeated application and removal of a splint-based stimulator. In this third-generation device, the components of the second-generation device were miniaturized and packaged into a device that has the dimensions, shape, size and configuration of a molar tooth. This device can be mounted on a commercially available Osseo integrated implant. The device comes with a wetness sensor embedded into the device to detect changes in wetness/dryness.

Third-generation implant-supported neuro-electro stimulating 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 neuro-electro stimulating device is shown in its applicator

(d) and mounted onto the root implant

(e) Clinical scenario after being placed

(f) Radiograph of the implant-supported device

Advantages

i. To generate continuous or frequent stimuli.
ii. To be applied into the oral cavity without interfering with regular oral functions
iii. To sense the wetness/dryness status of the oral cavity and automatically

increase/decrease the stimulus within a preset range (autoregulatory mode)

iv. To be controlled by the patient via a remote control.

The Osseo integrated implant is positioned in the region of the lower third molar (wisdom tooth). This ensures close proximity to the lingual nerve that carries both afferent and efferent salivary impulses and also not to interference with normal oral function. The Surgical aspect is pretty conventional, and the posterior location of the device is favored as it does not cause aesthetic concerns. (Figure 5).

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

A systematic review to analyze the recent advancements in the field of neurostimulation to treat xerostomia was conducted in 2019.[26] A total of 120 articles were identified through the search. After the elimination of the external and internal duplicates, only 52 articles were included. After reviewing titles and abstracts, only 22 articles were included. Animal studies confirmed that the application of electrical stimuli to this reflex arc increases saliva production and alleviates the symptoms of xerostomia.[27] Schneyer and Hall in their study reported that electrical neurostimulation in mice was more effective in replacing pilocarpine to induce saliva. Similarly, the use of electrical stimulation through the mucous membrane of oral cavity increases salivary production in patients with salivary gland hypofunction.[28,29,30] Hargitai *et al.* reported that application of externally placed pads over the parotid gland results in increased salivary production in normal and radiation-induced subjects with xerostomia.

Recent Advancements

Salipen - Salipen is the device which works on the principle of electrostimulation of salivary glands (Figure 6). It consists of two arms, both of which are flexible, and these arms, with the electrodes at the tip of each arm, are placed in the oral cavity, beneath the tongue.[11] This device deadens the feeling of dry mouth over time with no side effects and discomfort. The major advantage of this is that no electrical current is felt and the safety and efficacy of this method were proven in a number of clinical trials performed in many countries. This device is very easy to use and noninvasive. Patient compliance improved due to the ease of using this device.

Conclusion

Xerostomia is the primary clinical entity 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. Neuro-electrostimulation 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 neuro-electro stimulating 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-day.

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Table No. 1

Category	Generic Name
Anti Cholinergic Agent	Atropine
	Belladonna
	Benztropine
	Oxybutynin
	Scopolamine
	Trihexyphenidyl
Anti-depressant and anti-psychotic agent	
Selective serotonin reuptake inhibitor	Citalopram
	Fluoxetine
	Paroxetine
	Sertraline
	Venlafaxine

Tricyclic anti-depressants	Amitriptyline
	Desipramine
Heterocyclic anti-depressants	Imipramine
	Haloperidol
	Mirtazapine
Monoamine oxidase inhibitor	Pimozide
Atypical anti-depressants	Phenelzine
	Bupropion
	Nefazodone
	Olanzapine
Diuretic agents	Chlorothiazide
	Furosemide
	Hydrochlorothiazide
	Triamterene
Anti-hypertensive agents	Captopril
	Enalapril
	Clonidine
	Guanfacine
	Lisinopril
	Methyldopa
Sedatives 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
Anti-histaminic	Astemizole
	Brompherinamine
	Chlorpheniramine
	Diphenhydramine
	Loratadine
	Meclizine

Figures

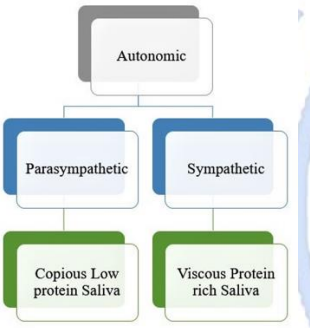

Figure 1

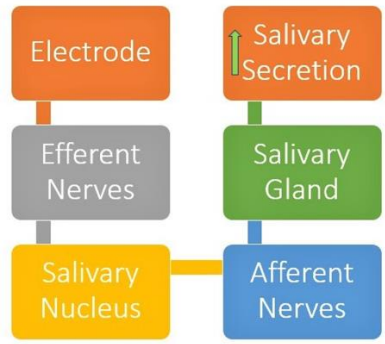

Figure 2

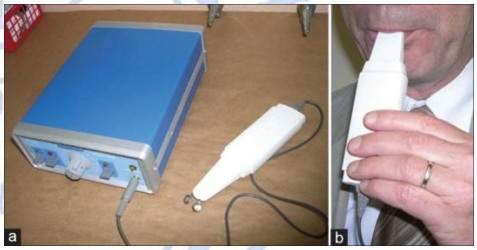

Figure 3

Figure 4

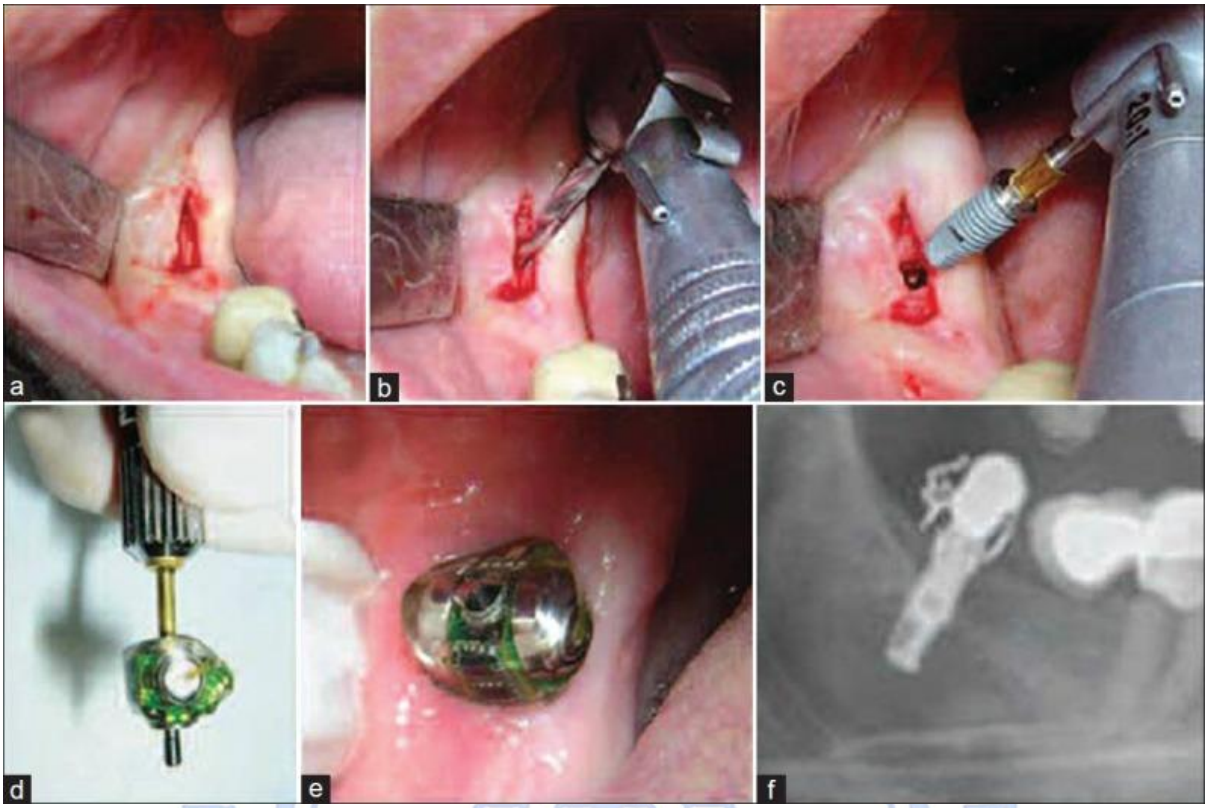

Figure 5

Figure 6