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Biotechnological advances in neuro-electro-stimulation for the treatment of hyposalivation and xerostomia

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Abstract

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. In the last years non-pharmacological treatments based on electro-stimulation for the treatment of xerostomia have been developed. This review is aimed at presenting new developments for the treatment of xerostomia, applying neuro-electro-stimulation by miniaturized intra-oral electro-stimulators. These devices increase salivary secretion and improve symptoms of oral dryness. Their effect is obtained by means of stimulation of the lingual nerve, in whose proximity the electrodes of the apparatus are placed. The objective of this mechanism is both to directly stimulate the salivary glands controlled by that nerve and to enhance the salivary reflex. Clinical studies have been carried out that have demonstrated the wetting effect of the method described in this article.

Key words: *Xerostomia, electro-stimulation, hyposalivation, saliva, dry mouth.*

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 the cases it results from salivary gland hypofunction (1). Population studies on xerostomia are based on questionnaires that investigate if and how frequently patients suffer from oral dryness. According to several reports, its prevalence in the adult population (i.e. people reporting that xerostomia afflicts them always or frequently), ranges between 10 and a 29%, affecting more women than men (2,3). Xerostomia is particularly prevalent among adults (4). Nevertheless, an increase of cases of xerostomía has been recently reported among young adults (5).

Upon meeting 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 active treatment is interrupted (6). Pharmacological agents, like pilocarpine HCl, have been studied extensively; nevertheless, more than one third of 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 (7,8). 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 (9).

The objective of this review is to present the most relevant clinical factors of xerostomia and the last advances of neuro-stimulation for its treatment, based on the accumulated knowledge of neurological control of salivary secretion.

Most common causes of xerostomia

Xerostomia can be caused by systemic diseases or iatrogenic effects. Diseases associated with salivary flow reduction include autoimmune diseases (particularly Sjögren's Syndrome), Alzheimer's disease, depression and diabetes. Infections caused by sialotrophic viruses such as hepatitis C virus (HCV) or human immunodeficiency virus (HIV), sarcoidosis, lymphoma or graft vs host disease can lead to inflammatory damage of salivary glands, which consequently generates dysfunction and xerostomia (10).

On the other hand, reduction of salivary flow can be induced by medical treatments, either medication intake, head and neck radiotherapy, chemotherapy or bone marrow transplantation (11,12). Nearly 400 medicines may lead to xerostomia as side effect (13). Among these drugs, it is worthwhile to mention: anti-cholinergic, anti-depression, anti-psychotic, anti-hypertensive, anti-diuretic, anti-histamine, and steroidal and non-steroidal anti-inflammatory agents, tranquilizers, muscular relaxants, and narcotic analgesics (14). The majority of those medications are taken during long periods of time and even for lifetime, and their deleterious effects increase along the intake period. The salivary flow is reduced significantly when two or more xerogenic medicines are taken simultaneously (15).

Alterations in the oral cavity in patients with xerostomia and hyposalivation

Xerostomía can be accompanied by a variety of changes in oral hard and soft tissues. Saliva fulfils important functions such as lubrication of the oral and oropharyngeal mucosa, as well as facilitating mastication, swallowing and formation of the nutritional bolus. In average, a healthy person produces 500 ml of saliva in a 24 hours period. Salivary flow-rate is 0,3 ml/min in resting condition, but it increases to 4 or 5 ml/min during mastication (1). The salivary fluid is crucial for defense against viral, bacterial and fungal infections, for remineralización of dental enamel and dentine and for taste sensation (16,17). Reduction in salivary flow-rate entails a compromise in oral defense mechanisms and lubrication; the oral mucosa can become painful, with burning sensation, ulcerated and atrophic. Frequently an increase in the rate of dental caries with a difficult to treat cervical decay pattern is observed (14). Patients with xerostomia complain about discomfort with prostheses and salivary microbiological changes saliva can induce oral candidiasis (16,18). However, a significant number of patients displaying hyposalivation lack dry mouth symptoms, rendering the clinical diagnosis of xerostomia even more difficult. The presence of associated clinical signs, such as extensive dental caries and candidiasis, must awake the suspicion that the patient suffers from xerostomia.

One of the most difficult to deal problems in patients with oral dryness is sleeping disturbance and consequently fatigue, which deteriorates quality of life and leads to social isolation of the patient (19).

Neurological control of salivary secretion

Salivary gland secretion is regulated by the autonomic nervous system. Acetylcholine agonists act on parasympathetic and muscarinic receptors of those exocrine glands inducing high electrolyte containing salivary secretion, whereas sympathetic stimulation produces the protein component of saliva. Thus, parasympathetic stimulation generates abundant saliva with low protein concentration and sympathetic stimulation produces little saliva with high protein concentration and viscosity (20).

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 (20,21).

The therapeutic potential of electro-stimulating nervous and muscular structures has been recognized in many areas of modern medicine. It is being used or investigated in a variety of clinical applications such as in bone healing or the treatment of pain, deafness, bladder dysfunction, cardiac arrhythmia (e.g. pacemaker), muscular weakness or denervation, problems of the respiratory system (e.g. phrenic nerve dysfunction), seizures, and essential tremor in Parkinson's disease (22).

Given the autonomic control of salivary secretion, a similar principle can be used in the management of salivary gland hypofunction and xerostomia. Application of electrical impulses on one, two or three components of the salivary reflex should improve both salivary secretion as well as several long term consequences of hyposalivation. Thus, a significant increase of salivary flow following electrical stimulation application in experimental animals has been observed (23). Application of an electrical current through the oral mucosa on afferent receptors and routes was reported in research projects aimed at increasing salivary flow and reducing oral dryness in patients with salivary gland hypofunction. It has been suggested that intra-oral electro-stimulation increments salivation in resting condition via the salivary reflex, i.e. through the production of efficient amounts of afferent-efferent stimuli (24,25).

Technological developments in salivary electro-stimulation

1- Mouthpiece with electrical cord

The outcome of the first attempt to implement neuro-electro-stimulation to increase salivary secretion was a device commercialized in the past in the USA (Salitron, Biosonics®, PA). The apparatus consisted of a mouthpiece and a video cassette recorder-sized external control module, both parts interconnected to each other by an electrical cord. The mouthpiece was hold by the user between the dorsal side of the tongue and the palate for several minutes every day. It generated a signal that stimulated the sensorial nerves of the oral mucosa and resulted in increased salivation (24,26). As the clinical results were promising with no side-effects, the device was approved by the Food and Drug Administration of the United States (FDA) in 1988. Nevertheless, it was not used massively due to its large size, high price and cumbersomeness for the user.

2- Self-contained electronic splint

In order to overcome the disadvantages of the Salitron® system, a consortium financed by the European Union developed a miniature intra-oral neuro-electro-stimulator to stimulate salivary flow (27).

The salivary neuro-electro-stimulator (Saliwell GenNarino®) is composed by a dental thermoplastic polyurethane-made apparatus and an electronic miniature stimulating device that contains a signal generator (electrodes), a battery and a circuit that is embedded within the plastic splint (Fig. 1). The electrodes are located on the third molar area mucosa to enable stimulation of the lingual nerve. The electro-stimulator is customized for each patient using the mold of its inferior dental arch. The system also contains a remote control that allows the patient to communicate with Saliwell GenNarino® by means of infrared light transmission at a wavelength of 940nm-950nm (Fig. 2). The GenNarino is similar to night guards to treat bruxism, is worn on the mandibular arch and is inserted and removed by the patient.

The distance between the surfaces of the electrodes and the lingual nerve can vary between 1 and 5 mm (28). In addition to the lingual nerve, also the long buccal nerve runs next to GenNarino's electrodes. As a result of exciting these nerves, all salivary glands are stimulated by the salivary reflex. Those nerves of the salivary reflex arch that are excited by the stimulating GenNarino are (underlined):

1- Taste buds of the anterior 2/3 of the tongue →*lingual nerve* → facial nerve → salivary center, from which efferent fibers can follow 3 pathways:

a) → facial nerve→*lingual nerve* →submandibular and sublingual glands.

b) → glossopharyngeal nerve →maxillary nerve → parotid gland.

c) →nerves to all minor salivary glands.

2- Mucosal sensorial receptors (tactile perception) →*lingual and long buccal nerves*→ trigeminal nerve → salivary center → efferent nerves to salivary glands according to the above description.

The following protocol has been developed for the clinical use of Saliwell GenNarino®:

1. Before taking impression for its preparation the clinician should verify that the dental, periodontal and oral mucosal status is optimal.
2. This system can be used by any patient with xerostomia.
3. In head and neck irradiated patients it is recommended to place the electrodes in the side that is contra-lateral to the irradiation area.
4. Irradiated patients and those treated with bisphosphonates require special precaution to avoid irritation-originated lesions. In case of mucosal ulceration, the device needs not to be worn until the lesion has healed.
5. GenNarino can replace pharmacological therapy; in

severe cases though, it can be used in combination with sialogogues, especially in patients with dry eye.
6. The patient must be controlled periodically.
7. Concomitant to this therapy, it is recommended to deliver optimal levels of fluorides in toothpastes and mouthwashes.
8. Its use in pregnant patients is not recommended. The use with other extra-oral electro-stimulation devices (e.g. pacemaker) seems to be safe.
9. This device needs to be replaced every year, when the battery runs out of power.

The short term effectiveness of this electro-stimulator in the treatment of the xerostomia was evaluated in a randomized, cross-over, double blind study, comparing the device in active state with the same apparatus in inactive state among patients with dry mouth symptoms due to diverse causes. The main objectives of this study were to assess the diminution of oral dryness (objectively verified by means of a wetness sensor incorporated in the device) and to establish improvement of symptoms related to xerostomia (by means of subjective measurement of the perception of oral dryness symptoms). The results of this study demonstrated that the device was well tolerated by all the patients and did not cause local or systemic adverse effects. Objective moistening ($p<0.0001$) and subjective decrease of patient-reported xerostomia ($p<0.005$) were registered (29). Thus, the electro-stimulator was effective in reducing oral dryness by its application during 10 minutes.

In order to confirm its long term effect and safety a multinational study is being carried out to evaluate its efficacy throughout a period of 12 months; the primary target is to verify if repeated neuro-electro-stimulation of salivary glands induces long term improvement in their function, as suggested in previous studies.

3- Miniature device supported by a dental implant

Some patients may require frequent and/or constant stimuli of salivary glands. Therefore, a dental implant-supported miniature neuro-electro-stimulator was developed (Saliwell Crown®, Fig. 3). The use of this fixed apparatus avoids the disadvantage associated with the use of a removable device. The components of the removable device were miniaturized in a small module, whose dimension and shape are similar to those of a molar tooth. It is adapted to commercially available dental implants. In addition, it contains a wetness sensor to detect changes in intra-oral moisture. This device provides neuro-electro-stimulation by generating continuous or frequent stimuli in the oral cavity without interfering with regular oral functions. The intensity and frequency of stimuli is auto-regulated (increased or decreased) by the device's ability to detect the oral wetness status, but also can be controlled by the patient activating the remote control.

The implant is placed in the inferior third molar area

Fig. 1. Saliwell GenNarino electrostimulator containing the electronic system embedded in the plastic splint.

Fig. 2. Electro-stimulator activation by the remote control.

Fig. 3. Clinical view of the miniature electro-stimulator supported by a dental implant located in the third molar area.

to assure proximity to the lingual nerve and to avoid interference with normal oral function and cosmetic concerns (Fig. 3). A clinical test is ongoing, aiming at evaluating the long term effect of this intra-oral neuro-electro-stimulator on salivary function and xerostomia symptoms. Results are promising and may render this salivary gland stimulating method to become the most convenient and safe means to treat xerostomia.

Conclusions and perspectives

Hyposalivation and xerostomia have multiple causes, but almost all, regardless of their aetiology, induce salivary flow reduction. Neuro-electro-stimulation of salivary glands overtakes a relevant role in therapeutic stimulation of salivation among patients requiring long term therapy and suffering from deteriorated quality of life. Intra-oral electro-stimulators offer a new non-pharmacological method for the treatment of oral dryness. Preliminary results showing increased salivary secretion and progressive improvement of xerostomia symptoms are demonstrating the effectiveness of these intra-oral devices for neuro-electro-stimulation.

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