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Perspective

Saliva Electro-stimulation Devices (SEDs) for the Management of Xerostomia: An update.

Dispositivos de electroestimulación de saliva (SED) para el tratamiento de la Xerostomía: Una actualización.

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The aim of this manuscript is to provide an overview of the past and current approaches for saliva stimulation with electro-stimulation devices (EDs) for the management of xerostomia. There are many causes and factors affecting the performance of salivary gland secretion, systematic or pathological, which compromise the lifestyle of the patient with long-term consequences that will impair health.

Saliva contains a combination of many proteins, enzymes and peptides which helps in digestion, defense, and lubrication of the oral cavity. There are exceptionally good outcomes reported in the last few years from devices used to stimulate saliva via electronic impulses.

INTRODUCTION.

Human saliva plays an essential role in the maintenance of the oral cavity, such as inhibiting the demineralization of tooth tissues and helping in their remineralization, lubricating the oral mucosa, aids in buffering, for the digestion of food, tasting food, and in speech.[1,2] Saliva can also contain microorganisms, including viruses such as the Zika virus[3] and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among many others.[4,5]

Saliva contains numerous proteins and peptides such as defensins,[6] cathelicidins,[7] histatins,[8] statherin, adrenomedullin, and neuropeptides.[9] The daily normal secretion of saliva ranges from 0.25 to 0.35 mL/min, thus, lower rates will cause a condition known as xerostomia, characterized by dry mouth, a burning sensation, and difficulty in swallowing.

The classification of xerostomia is based on its pathogenesis: true xerostomia, due to malfunction of the salivary gland; while, symptomatic xerostomia, results in oral dryness despite normal salivary gland function.[10] It is most commonly found in females and affects about 46% of the world population currently.

Historically, the concept of nerve stimulation through electronic devices has been reported in many areas of medicine such as wound healing, muscular pain relief, deafness, bladder dysfunction, seizures, tremors in Parkinson's disease, cardiac arrhythmia (pacemakers), and phrenic nerve dysfunction. Experimental saliva electronic stimulator used for xerostomia treatment was first reported in 1986 by Professor William W Weiss, in the USA. In this innovative study, twenty-four patients were selected and evaluated after three weeks. This non-invasive electro-stimulation

device induced the production of saliva physiologically in xerostomia patients by a mechanism of stimulating tactile receptors, taste receptors and intrinsic muscle mechanoreceptors (within the mucosa of the dorsum of the tongue and the roof of the mouth).[11]

After this groundbreaking event, another group of researchers and manufacturers introduced novel approaches and performed human clinical trials.There are numerous diseases like diabetes, Sjögren's syndrome, carcinoma of salivary glands, anxiety and depression that are associated with xerostomia and the hypofunctioning of salivary glands. Some external factors also contribute to hyposalivation, such as radiation therapy, chemotherapy, and xenogeneic drugs.

Mechanism of Action of SEDs

The saliva electrostimulation devices (SED) mechanism of action (MOA) is not fully understood but it has been suggested that electrical impulses on one or more salivary reflex provoke salivary secretion, and also helps in the management of long term consequences of hyposalivation. The physiological control and management of salivary secretion is via the reflex arc. The pathway of reflex arc comprises of:

(i) afferent nerves, which carry impulses generated by taste receptors and masticatory activities; to

(ii) CNS: which consists of salivary center (in medulla oblongata, brain), the central unit of processing and generating regulatory impulses in responses; and

(iii) efferent nerves, which conduct regulatory impulses to the oral cavity and control parasympathetic and sympathetic salivary secretion by influencing function of acini (secretory cells) and the blood supply of salivary glands. Concept of electrostimulating devices in the management of dry mouth is classified by two different approaches: According to location of the device, and according to generation of the devices. (Figure 1).

The first-generation saliva electro-stimulation device consists of a hand-held probe, tipped with stainless steel electrodes, and a control panel that houses the electronic signal generating power source and a battery, The devise was manufactured by Biosonics "SAL" Salivator System™ (Philadelphia, Pennsylvania, USA) and was approved by the US Food and Drug Administration in 1988 as no adverse effects were reported (local or systematic). The electrode probe of the device was first placed on the dorsum of the tongue (Figure 2A and Figure 2B). The patient is then instructed to seal their lips to induce muscle contraction; in this way the electrode will touch the palate and tongue. After a few minutes, this stimulating signal results in an immediate response for saliva secretion. Weiss *et al.*,[11] reported no adverse effects after 1 to 3 minutes, stimuli were administered to 24 patients with Sjögren's syndrome (SS) or a history of head and neck radiation therapy.

Figure 1. Classification of saliva electro-stimulation devices for xerostomia treatment.

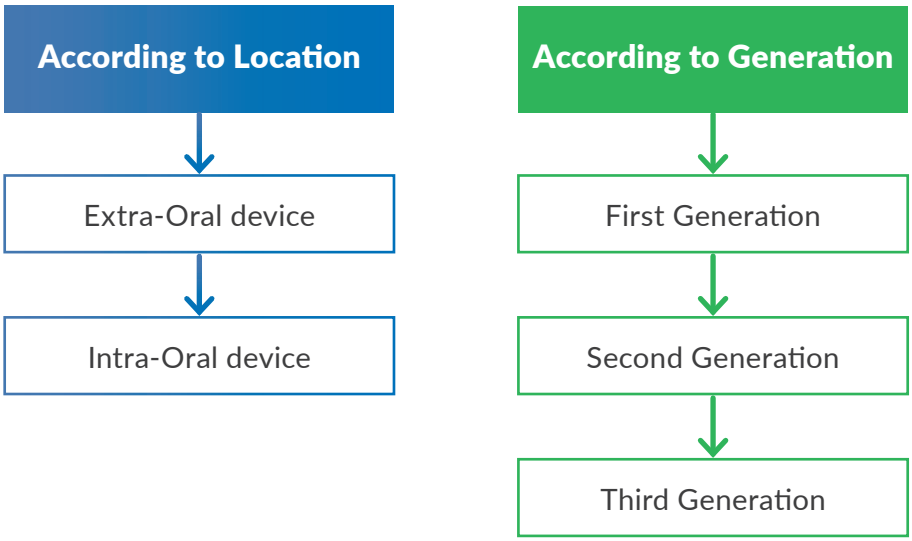

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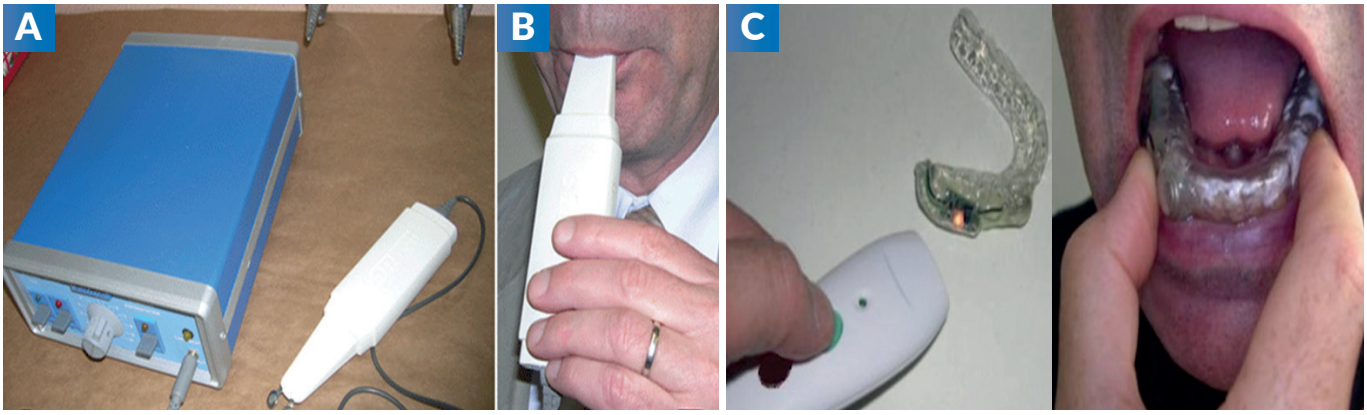
Figure 2. Saliva electrostimulation device (SED).



A: Consists of a console that hosts a battery and electronic signal generating power sourc.
B: Hand- held probe with stainless steel electrodes. **C:** Saliwell GenNarino® saliva electrostimulating intra oral device.

Figure 3. SaliPen is a saliva electrostimulating device (SEDs) with two flexible arms. The SaliPen is used for up to 5 minutes easily at home (pictures provided by Saliwell Ltd).

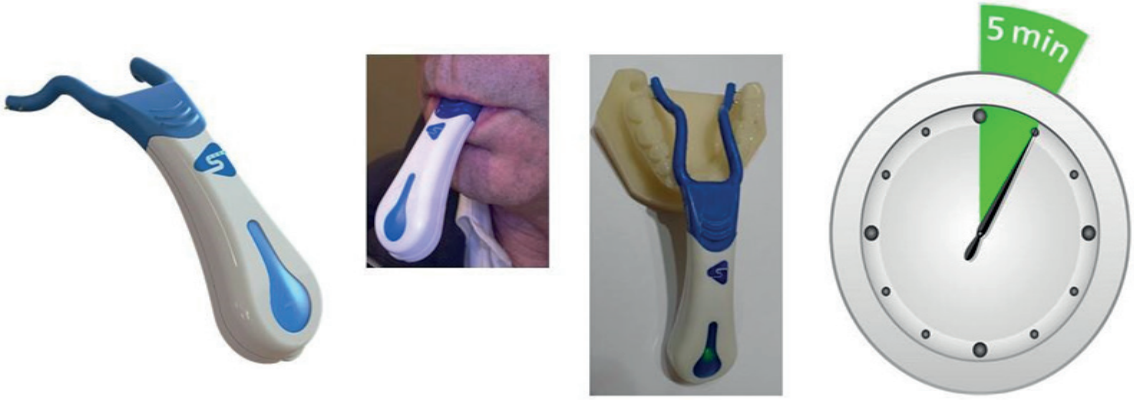


Figure 4. Active dental implant: Artificial tooth containing wetness sensor, battery and an electrostimulation unit for stimulating secretion of saliva

Oral wetness was analysed by sweeping a gloved finger on buccal mucosa, floor of the mouth, tongue, and palate, a dental chair light was used to check for moisture present on finger, thus reflecting a positive sign of moisture. This study only concluded the increased flow in saliva production and removal of symptomatic improvements; however, it lacks qualitative saliva analysis. Steller *et al*.,[12] used the same approach for the analysis of 29 Sjögren's syndrome patients and reported that some patients with residual salivary flow showed a significant response to electrical stimulation but others with low or absent whole saliva flow rates did not respond.

Sialometry was used in this study to check the pre- and post-stimulation of the whole saliva flow rate, with results of 0.20g/2 min and 0.46g/2 min recorded. Talal *et al*.,[13] demonstrated the clinical effectiveness of electrostimulation on salivary glands of 77 patients of Sjögren's syndrome.All subjects were assigned active devices and were instructed to place the electrode's probe at the midline of the tongue, about 3/4 inch from the tip then positioning the electrodes between the tongue and the roof of the mouth for 3 min thrice a day (automatically set). This study was conducted for four weeks and visits were scheduled as week 1, 2, 3, and 4, in every visit, expectorated saliva was collected for assessing the flow rate before and after using the device. The use of this generation of SEDs was limited due to its high price, size and not being user friendly.

A novel technique was reported in 1998 *"Acupuncture with low frequency electronic stimulation"*, in which xerostomia patients were treated with manual acupuncture with low frequency (2-Hz) electrical stimulation for sensory stimulation, leading to increased saliva production in patients with dry mouth.[14] This study also recorded the release of neuropeptide in saliva.

The Saliwell Study Group developed a second generation of SEDs known as GenNarino® with the help of European Commission-funded research consortium to overcome the disadvantages of first generation SEDs.[15] The apparatus that houses this device is made of dental thermoplastic resin, similar to a mouth guard used to treat bruxism and temporomandibular joint disorders. It contains electrodes, stimulating circuit, infrared receiver, moisture sensor and a battery that is embedded within the resin appliance (Figure 2C).

This appliance is constructed in a way that efferent neural pathways of submandibular and sublingual glands are stimulated by electrodes without any deviation, they are embedded in the third molar mucosal area for the stimulation of the lingual nerve. The distance between the lingual nerve and the surfaces of electrodes are 1mm to 5mm and the long buccal nerve is excited due to close proximity of the electrodes. Microcontroller programming is particularly important to control the stimulation parameters such as amplitude, pulse width, frequency of stimulation and number of pulses per burst. Infra-red (IR) light transmission at a wavelength of 940nm-950nm was built-in for patient comfortability to communicate with the GenNarino® through remote control.

Randomized clinical trials of pilocarpine ,[16] cevimeline,[17] and intra-oral electrostimulation were conducted to evaluate and compare the effectiveness and safety and concluded that xerostomia severity was best improved by electrostimulation during the first four weeks as compared to drugs.[18] Meaningful oral mucosal membrane moistening was listed objectively (p<0.0001) and a decrease in patient-reported dryness (p<0.005) was reported. This device is contraindicated in pregnancy, mucosal ulceration, and cardiac dysfunction, and internally transplanted medical devices such as pacemakers. Frequent complications influencing long term survivors of allogeneic hematopoietic cell transplantation is chronic graft-*versus*-host disease (cGVHD) with patients presenting clinically with oral mucosa (buccal, lingual and tongue) and salivary gland damage.[19,20]

Salivary glands damage will result in reduced salivary secretion. Recommended treatment for this situation is oral moisturizing agents, systematic sialogogues, and tropical preparations but the required frequent use entails side effects. One study evaluated the safety and efficacy of an intra-oral electro stimulator for the relief of xerostomia in patients cGVHD.

The study consisted of six patients with cGVHD and provided a four-weeks treatment plan; this study design was a sham-controlled, double-blind, and randomized cross-over study. During this study two subjects were hospitalized due to serious adverse events. However, these reported adverse effects were not due to the tested device. This case series study suggested that this device is safe in oral cGVHD patients and resulted in objective and subjective

improvements in xerostomia patients.[21]

Another patented device was by Saliwell Ltd®, named "SaliPen". The SaliPen uses electrostimulation to increase saliva production. The SaliPen device is a patented "one size fits all" product with an embedded electronic module that is worn typically for only a few minutes every day. (Figure 3)

The SaliPen has two flexible arms that are placed in the mouth. The picture in the center displays the arms that contact the inner gums of the lower wisdom teeth, underneath the tongue. The rest of the device stays outside the mouth. The device treats dry mouth by intraoral low-intensity electrostimulation that is not felt by the patient. The electrostimulation is delivered by the tips of the arms to the nerves that control the salivary gland activity and causes salivary glands to produce more saliva. When more saliva is produced, the dry mouth sensation declines. The concept of designing dental implant supported electrostimulating devices to treat xerostomia was adopted from medically used devices such as pacemakers for cardiac arrhythmia, and phrenic nerve stimulators for respiratory malfunction. This device was developed by Saliwell Crown®, Saliwell Ltd., Harutzim, Israel (Figure 3).

This device was mounted on commercially available dental implants and positioned in the mandibular third molar region close to the lingual nerve, as the lingual nerve carries both efferent and afferent salivary impulses. A few patient needs are not covered by removable SEDs, so this device provides frequent or constant stimulation to salivary glands without interfering in the regular function of oral cavity.

The components of this osseointegrated device are electric circuit, two 1.5 V batteries, a microprocessor, a wetness sensor, stimulating electrodes, and infra-red (IR) receiver, all these components are consoled in an epoxy-made embodiment. The Saliwell crown device consists of one additional component in the interface with the dental implant, for a secure and easy-to-handle means of inserting into, holding onto, and detaching from. This device is quite smooth with no sharp edges that could cause irritation of soft tissues.

Lafaurie *et al.*,[22] reported that clinical testing is ongoing for the evaluation of the long term effects on salivary function and xerostomia treatment. They are aiming for promising results and this could be the most convenient device for the treatment of xerostomia.

One study reported that Saliwell Crown® placed on an 81-year old female patient with complaints of dry and burning mouth, gave promising results when evaluated by salivary tests and self-assessment questionnaires.[23]

Figure 4 shows the representation of the active dental implant device developed by a Fraunhofer Institute for Biomedical Engineering (IBMT), Germany. The manufacturer claims that an active implant device for saliva stimulation is a good and promising model suitable for xerostomia patients.

CONCLUSION.

Xerostomia effects 5.5% of the population and may develop serious health issues in the adult population. Natural ingredients, pharmacological drugs and electrostimulation devices may control this condition. The future of electrostimulation devices appear to be very promising and new innovations are still possible within same generation technologies for development of new possibilities.

Miniaturization, efficient and space-saving powering, wireless power, and data transfer between external and implanted modules as well as innovations in encapsulation and housing are key issues for the future of saliva electrostimulation devices (SEDs).

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REFERENCES.

1. Khurshid Z, Zohaib S, Najeeb S, Zafar MS, Slowey PD, Almas K. Human Saliva Collection Devices for Proteomics: An Update. Int J Mol Sci. 2016;17(6):846.
2. Khurshid Z, Moin SF, Khan RS, Agwan MAS, Alwadaani AH, Zafar MS. Human salivary protein extraction from RNAPro•SAL™, Pure•SAL™, and passive drooling method. Eur J Dent. 2017;11(3):385-389.
3. Khurshid Z, Zafar M, Khan E, Mali M, Latif M. Human saliva can be a diagnostic tool for Zika virus detection. J Infect Public Health. 2019;12(5):601-604.
4. Hamid H, Khurshid Z, Adanir N, Zafar MS, Zohaib S. COVID-19 Pandemic and Role of Human Saliva as a Testing Biofluid in Point-of-Care Technology. Euro J Dent. 2020.
5. Khurshid Z, Asiri FYI, Al Wadaani H. Human Saliva: Non-Invasive Fluid for Detecting Novel Coronavirus (2019-nCoV). Int J Environ Res Public Health. 2020;17(7):2225.
6. Khurshid Z, Zafar MS, Naseem M, Khan RS, Najeeb S. Human Oral Defensins Antimicrobial Peptides: A Future Promising Antimicrobial Drug. Curr Pharm Des. 2018;24(10):1130-1137.
7. Khurshid Z, Naseem M, Yahya I Asiri F, Mali M, Sannam Khan R, Sahibzada HA, Zafar MS, Faraz Moin S, Khan E. Significance and Diagnostic Role of Antimicrobial Cathelicidins (LL-37) Peptides in Oral Health. Biomolecules. 2017;7(4):80.
8. Khurshid Z, Najeeb S, Mali M, Moin SF, Raza SQ, Zohaib S, Sefat F, Zafar MS. Histatin peptides: Pharmacological functions and their applications in dentistry. Saudi Pharm J. 2017;25(1):25-31.
9. Khurshid Z, Naseem M, Sheikh Z, Najeeb S, Shahab S, Zafar MS. Oral antimicrobial peptides: Types and role in the oral cavity. Saudi Pharm J. 2016;24(5):515-524.
10. Tanasiewicz M, Hildebrandt T, Obersztyn I. Xerostomia of Various Etiologies: A Review of the Literature. Adv Clin Exp Med. 2016;25(1):199-206.
11. Weiss WW Jr, Brenman HS, Katz P, Bennett JA. Use of an electronic stimulator for the treatment of dry mouth. J Oral Maxillofac Surg. 1986;44(11):845-50.
12. Steller M, Chou L, Daniels TE. Electrical stimulation of salivary flow in patients with Sjögren's syndrome. J Dent Res. 1988;67(10):1334-7.
13. 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(2):43-5.
14. Dawidson I, Angmar-Månsson B, Blom M, Theodorsson E, Lundeberg T. The influence of sensory stimulation (acupuncture) on the release of neuropeptides in the saliva of healthy subjects. Life Sci. 1998;63(8):659-74.
15. Koch KP, Steinmetz O, Velten T, Beiski BZ, Wolff A, Hoffmann, KP, and the Saliwell Study Group: "Stimulation device for Saliva stimulation."11th Annual Conference of the International Functional Electrical Stimulation Society in Miyagi-Zao (Japan), 280-282 (2006).
16. LeVeque FG, Montgomery M, Potter D, Zimmer MB, Rieke JW, Steiger BW, Gallagher SC, Muscoplat CC. A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. J Clin Oncol. 1993;11(6):1124-31.
17. Witsell DL, Stinnett S, Chambers MS. Effectiveness of cevimeline to improve oral health in patients with postradiation xerostomia. Head Neck. 2012;34(8):1136-42.
18. Strietzel FP, Martín-Granizo R, Fedele S, Lo Russo L, Mignogna M, Reichart PA, Wolff A. Electrostimulating device in the management of xerostomia. Oral Dis. 2007;13(2):206-13.
19. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versushost disease. Biol Blood Marrow Transplant. 2003;9:215-33.
20. Higman MA, Vogelsang GB. Chronic graft versus host disease. Br J Haematol. 2004;125(4):435-54.
21. Zadik Y, Zeevi I, Luboshitz-Shon N, Dakwar N, Wolff A, Shapira MY, Or R, Elad S. Safety and efficacy of an intra-oral electrostimulator for the relief of dry mouth in patients with chronic graft versus host disease: Case series. Med Oral Patol Oral Cir Bucal. 2014;19(3):e212-9.
22. Lafaurie G, Fedele S, López RM, Wolff A, Strietzel F, Porter SR, Konttinen YT. Biotechnological advances in neuro-electro-stimulation for the treatment of hyposalivation and xerostomia. Med Oral Patol Oral Cir Bucal. 2009;14(2):E76-80.
23. Ami S, Wolff A. Implant-supported electrostimulating device to treat xerostomia: a preliminary study. Clinical Implant Dentistry and Related Research. 2010;12(1):62-71.