Implant-Supported Electrostimulating Device to Treat Xerostomia: A Preliminary Study

Smidt Ami, DMD, MSc, BMedSc;* Andy Wolff, DMD†

ABSTRACT

Background: The full accomplishment of salivary function depends on proper salivary flow rate and composition. Salivary secretion is highly essential in the maintenance of health and integrity of oral hard and soft tissue. Xerostomia is a common symptom affecting between one-fifth and one-third of the adult population, more commonly women than men. Induction of salivary secretion exists in several pharmacological formulations per os. Electrostimulation to enhance salivary secretion has been used frequently as a research tool but only in limited extent as a clinical method to treat patients with xerostomia.

Purpose: The aims of this preliminary study were to observe and evaluate the therapeutic effect on xerostomia of the Saliwell Crown (Saliwell Ltd., Harutzim, Israel), an innovative saliva electrostimulation device fixed on an implant, placed in the lower third molar area.

Materials and Methods: A Saliwell Crown was placed in the lower third molar area of an 81-year-old female patient with complaints of dry and burning mouth. Salivary secretion was measured, and the patient was asked to fill in written satisfaction questionnaires. The patient was monitored for a year, comparing her salivary secretion rates and the written questionnaires.

Results: The results showed a constant slight but significant increase in the salivary secretion and in the patient's personal feelings as presented in the questionnaires.

Conclusions: The saliva stimulation device Saliwell Crown, placed on an implant in an 81-year-old patient with dry and burning mouth complaints, presented promising results when both the salivary secretion tests and the self-assessment questionnaires were examined and compared.

KEY WORDS: dry mouth, electrostimulator, implant, saliva, xerostomia

INTRODUCTION

Saliva performs a crucial role in the oral cavity. The full accomplishment of salivary functions depends on proper salivary flow rate and composition. Taste perception is facilitated by saliva carrying food particles onto the taste buds in an appropriate dilution. Salivary amylase and lipase start the digestion of starch and fat.[1] Saliva is also important in the formation of the food bolus, and the salivary lubricatory glycoproteins permanently coat oral surfaces, assisting in food mobility and reducing friction between the different oral structures (teeth, tongue, cheeks, lips) and between these structures and foreign elements (food, dental prostheses).[2] Salivary lubrication, repair, lavage, antimicrobial, and buffering properties contribute significantly to the maintenance of oral hard and soft tissue integrity.[3]

Human beings possess three pairs of major salivary glands. Two of them (parotid and submandibular glands) secrete the greatest part of saliva,[4] while the third one (sublingual glands) and a myriad of minor salivary glands spread throughout the oral mucosa[5] and provide a minor share of oral fluid.

Salivary secretion fluctuates between minimal and maximal rates. The basal secretion of saliva, which is a result of the spontaneous activity of the salivary nuclei, displays a circadian rhythm of high amplitude.[6,7] The secretion of saliva is regulated by the autonomic nervous system, with a minor role played by hormones and

*Head, The Center for Graduate Studies in Prosthodontics, Department of Prosthodontics, Faculty of Dental Medicine, The Hebrew University – Hadassah, Jerusalem, Israel; †President, Saliwell Ltd., Harutzim, Israel

Reprint requests: Dr. Ami Smidt, 6 Levitan St., Neve Avivim, Tel Aviv, 69204, Israel; e-mail: smidta@cc.huji.ac.il

DOI 10.1111/j.1708-8208.2009.00180.x

autocoids. While both autonomic divisions act synergistically to produce salivation by the salivary glands, the parasympathetic system is mostly responsible for the water and electrolyte secretion, and the sympathetic system mainly regulates the protein (eg, amylase) secretion.[8,9] The range of normal flow rates in unstimulated conditions is from 0.2 to 0.5 mL/min, and that of the stimulated flow rate is from 0.9 to 2.6 mL/min.[10]

The stimuli that enhance salivation are related to eating: tasting, smelling or seeing food, and chewing.[7,11–13] During meals, saliva production rises 5- to 50-fold over basal secretion.[14] These peripheral stimuli are transmitted by afferent nervous fibers to the central nervous system, which in turn reacts and upregulates salivary secretion via efferent salivary fibers.[15]

Xerostomia is the symptom of oral dryness resulting most frequently from salivary gland hypofunction (SGH).[4,16,17] SGH generates xerostomia when salivary flow does not suffice to compensate for loss of fluid from the mouth. Oral fluid is lost by swallowing, absorption by the oral mucosa, and evaporation from the mouth.

Xerostomia is a common symptom and may affect between one-fifth and one-third of the adult population. It is known to affect women more commonly than men.[16,18,19]

When caused by SGH, xerostomia may be accompanied by a variety of oral hard and soft tissue changes. The lower the salivary flow rate, the less salivary defense and lubrication components enter the oral cavity. The mucosal tissues may become painful, "burning," ulcerated, or atrophic. An increased rate of dental caries with a distinctive cervical pattern of decay, which is extremely difficult to treat, is typically seen.[4,20] Denture wearing in xerostomia is usually associated with severe discomfort in such patients exhibiting high prevalence of oral candidiasis.[21,22]

Functional oral disturbances appear in situations with decreased salivary secretion. Chewing, swallowing, and speaking are difficult, and taste sensation may be severely affected.[4,16] Patients with xerostomia interrupt their sleep repeatedly to sip water. Xerostomia can be accompanied by oral burning sensations.[23] These disorders affect significantly the general quality of life and well-being of these individuals.

Not all cases of SGH are symptomatic and are perceived as xerostomia. Xerostomia is thought to become a significant symptom when the unstimulated flow rate is reduced by 50% or more.[7] Other symptoms that have been related to SGH are halitosis (bad breath) and burning mouth syndrome.[24,25] Those disorders are the source of significant complaints that often lead to reclusion and loneliness.

SGH can be caused by systemic disease or by its treatment. Examples of the former include autoimmune diseases such as Sjögren's syndrome (SS), an autoimmune disease causing oral and ocular dryness and the second most frequent cause of SGH. Both types, primary and secondary SS, are most frequently diagnosed among women older than 40 years[26] and among those with Alzheimer's disease,[27] depression,[8,9] diabetes,[28] and others. Medical treatments that can induce SGH are intake of medications, head and neck radiotherapy, chemotherapy, and bone marrow transplantation.[4,5,7,26,29,30]

An electronic stimulator was introduced to the US market in the late 1980s, presenting promising results with no adverse effects.[31] It was not accepted by the market because of its size and being cumbersome, and difficulties in achieving constant stimulation.

RATIONALE OF AN IMPLANT-SUPPORTED ELECTROSTIMULATOR OF SALIVATION

The principles for xerostomia treatment, established by the Commission on Oral Health, Research and Epidemiology of the Federation Dentaire Internationale[32] are as follows:

- Stimulation of secretion has the great advantage of providing the benefits of natural saliva.
- Development of a sustained-acting preparation would be ideal for longer-term management of the patient with dry mouth, who is bound to remain a chronic patient.

The presented device (Saliwell Crown, Saliwell Ltd., Harutzim, Israel) is aimed at fulfilling those principles by electro-stimulating salivation through the excitation of relevant nerves in the area of the lower third molar tooth. The stimulating device is mounted on a commercially available dental implant (Figure 1).

Electrostimulation with implanted devices is not a new concept, and is in use or under investigation for a variety of other conditions, such as the treatment of pain, deafness, bone healing, micturition (urination) disorders, cardiac arrhythmia (pacemakers), muscle weakness or denervation, respiratory malfunction (phrenic nerve stimulator), seizures, and essential or parkinsonian tremors.

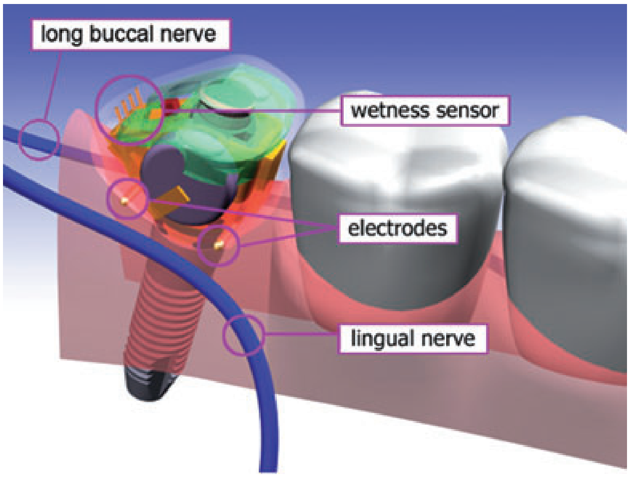

Figure 1 An overview on the location of the Saliwell Crown and the different nerves responsible for stimulation of salivation.

The fact that the nervous system controls the secretion of saliva became evident with Ludwig's discovery in 1850 that electrical stimulation of the chorda tympani-lingual nerve in the dog caused a copious secretion of submandibular saliva. Since then, electrostimulation of nerves involved in the salivary secretory process has been extensively used in animal experiments. Some of the reported electrical parameters used to excite the nerves are: frequency of 0.1 to 20 Hz, pulse duration of 2 to 5 ms, voltage of 3 to 40 V.[33–42] Initial human experiments using electrodes attached to a removable dental appliance have shown significant increase in salivation without side effects, even no tingling or discomfort.[43]

The impulses that travel through the nerve fibers involved in the salivary reflex follow two directions: the afferent ones go from the sensory organs to the salivary centers in the central nervous system, whereas the efferent fibers are directed from the salivary centers to the salivary glands. The electrical signals are delivered by the Saliwell Crown to the surrounding tissues, inclose proximity (1–5 mm) to the lingual and long-buccal nerves,[44,45] by electrodes placed on the surface of the electro-stimulator. In addition, also the inferior alveolar nerve may be reached by the delivered electrical current. The pathways of these nerve fibers and those potentially stimulated by Saliwell Crown depicted in **bold letters**[46] are as follows:

- Taste buds on anterior two-thirds of the tongue – **lingual nerve** – facial nerve – salivary center – facial nerve – **lingual nerve** – submandibular and sublingual glands.
- Taste buds as above – **lingual nerve** – facial nerve – salivary center – glossopharyngeal nerve – maxillary nerve – parotid gland.
- Taste buds as previously described – **lingual nerve** – facial nerve – salivary center – nerves to all minor salivary glands.
- Mucosal sensory receptors (tactile perception) – **lingual and long buccal nerves** – trigeminal nerve – salivary center – nerves to salivary glands as previously described.
- Masticatory proprioceptors – **inferior alveolar nerve** – trigeminal nerve – salivary center – nerves to salivary glands as previously described.

As can be appreciated, all salivary glands can be potentially stimulated as a result of the excitation of the lingual, long buccal, and inferior alveolar nerves.

The European Commission Framework Programme V of the European Union has funded a project (acronym: SALIWELL; official full name: "Intelligent micro-sensor, electroactuated, stimulator of salivary glands," Contract no.: IST-2001-37409) that has developed an intraoral electrostimulator of salivary glands to treat dry mouth. The device, named Saliwell GenNarino (Saliwell Ltd., Harutzim, Israel), is a removable appliance, combining microelectronics, software, and wireless communication, and applies stimulating signals on the lingual nerve, leading to enhanced salivary secretion. The device, containing electrodes, a wetness sensor, an electronic circuit, and a power source, was tested on xerostomic individuals in a crossover, randomized, sham-controlled, double-blinded study.[43] Electrical stimulation and sham were delivered during 10 minutes to the oral mucosa, in the mandibular third molar region. Oral wetness was measured by the wetness sensor. As primary outcome, changes in oral wetness were assessed and compared between active and sham modes. In addition, subjective patient evaluation of device's efficacy and side effects was recorded. After the performance of 158 experiments, electrostimulation (in contrast to an opposite effect of sham) resulted in a significant increase in oral wetness ($p < .0001$), leading to a beneficial effect on patients' subjective condition ($p < .05$). No significant side effects were observed. The results suggest that intraoral delivery of low-current electrostimulation has the potential to relieve symptoms of xerostomia by increasing oral wetness.

An ongoing randomized multinational crossover clinical trial, with the use of the GenNarino removable device (shaped as a mandibular mouth guard) is conducted, comparing between active versus a sham mode, in a double-blind design. In contrast to the lack of significant effects resulting from the use of the sham device, the active device proved to induce a significant improvement in a variety of xerostomia-related parameters. Seven patients out of the group examined started the study with no detectable salivary flow rate. Interestingly, unstimulated and stimulated salivas could be collected after active GenNarino usage among five of them, of which one was with dry mouth as a result of radiotherapy to the head and neck. In contrast, evaluation after 1 month of sham use showed secretion to be null (A. Wolff, personal communication, October 2008).

MATERIALS AND METHODS

The system consists of two major elements: the Saliwell Crown and an infrared (IR) remote control unit (a standard, commercially available remote control unit), which enables the clinician to communicate with Saliwell Crown by IR light transmission (wavelength between 940 and 950 nm). Saliwell Crown is a fixed-removable dental appliance comprising (1) an adapted abutment manufactured by Nobel Biocare AB, Göteborg, Sweden, and (2) a miniature electronic module manufactured by Valtronic SA, Les Charbonnieres, Switzerland. Saliwell Crown is mounted on a commercially available dental implant. The device can be inserted, removed, or replaced by a clinician using the regular implant tools.

The Saliwell Crown is placed in the lower third molar area, in vicinity to the lingual nerve. The Crown is aimed at exciting this and other nerves present in that area, with the objective of stimulating the activity of the salivary glands. The electric pulses delivered by the Crown will spread through the surrounding tissues to finally reach the nerves.

The Saliwell Crown is composed of an electric circuit, two 1.5 V batteries, a microprocessor, a wetness sensor (not activated in this trial), an IR receiver, and stimulating electrodes. All these elements are encapsulated in an epoxy-made embodiment. An additional component of the embodiment is the interface with the implant, designed to provide for a secure and easy-to-handle means of inserting to, holding to, and detaching from, the dental implant. The Saliwell Crown device has a smooth texture on all surfaces with no protruding sharp-shaped hard elements that may cause irritation. The electrodes are placed in such a way to contact the oral tissue that surrounds the cervical portion of the Crown (the part that is nearest to the dental implant).

Figures 1 and 2 provide a diagrammatic presentation of the Saliwell Crown and its relation to the bone when placed on an implant.

Unstimulated and paraffin-chewing-stimulated whole salivas were collected by expectoration into special tubes for 5 minutes. Collections were performed at the same time of the day throughout the entire trial. Saliva volume was determined gravimetrically (assuming a specific gravity of 1), and, thereafter, the flow rate was calculated by dividing the volume by 5.[10]

The following questionnaire was completed by the patient. On each of the first five questions, the distance of the marked tick to 0 on a 100-mm-long visual analog scale was measured and registered.[47,48]

- How do you rate your quality of life today?
  Extremely bad (0) ----------------------- (10) Perfect
- How dry is your mouth today?
  Extremely dry (0) --------------- (10) Not dry at all
- How burning is your mouth today?
  Extremely burning (0) ---------- (10) Not burning
- How difficult is it for you to speak because of your dry mouth?
  Extremely difficult (0) ----------- (10) Without any problem
- How difficult is it for you to swallow because of your dry mouth?
  Extremely difficult (0) -------------- (10) Without any problem
- During the past week, how many times on average did you wake up in the night because of the dryness in your mouth?

Clinical Case Report

A female patient, 81 years of age, entered the clinic with a complaint of dry and burning mouth. The patient reported on loss of taste and difficulties in chewing and in holding her upper full denture. In the lower jaw, the patient had a removable telescopic denture seating on 6 abutment teeth. The patient reported on a transient cerebrovascular attack some 4 years before entering the clinic. The patient received since the event treatment against depression, and the intake of such medication in

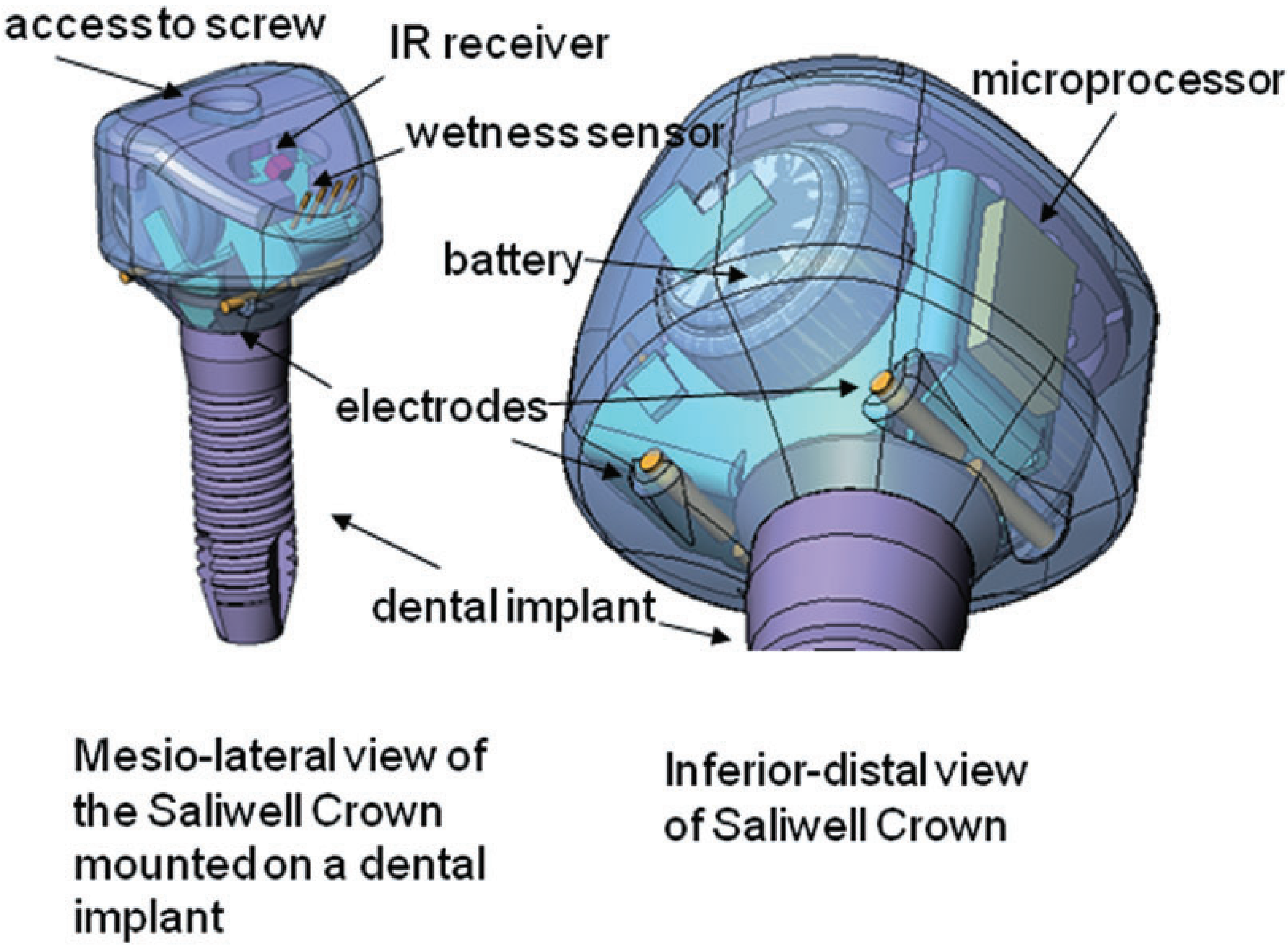

Figure 2 Two views of the device, presenting two round batteries, the wetness sensor, the IR receiver, the electrodes, the microprocessor, the dental implant, and the access to the screw.

this case is known to induce dry mouth and SGH.[5,7,29] Salivary secretion tests measurements presented low amounts in unstimulated and stimulated saliva flow rate tests. In accordance to the well-recognized fact that increased age is mostly accompanied by coexistent diseases and medication intake,[49,50] the cause for the xerostomic symptoms in this case was the extensive use of medication, that is, more than one hyposalivatory drug taken simultaneously.[51,52] The patient was using an anti-hypertensive and a tranquilizing agent (Bisprolol fumerate [Rafa Laboratories Ltd., Jerusalem, Israel], a beta blocker, 10 mg daily and Diazepam [Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel] 30 mg daily) all known to affect salivary flow.[53]

Salivary supplements were tried in the past, along with "sucking pills" for the relief of xerostomia, with no success. Also, wetting with artificial salivary supplements was reported to be unsatisfactory. All these treatments were found hardly effective even immediately after use. The patient was unable to chew a gum. Pilocarpine was not prescribed because of a history of heart disease and gastrointestinal problems.[5,17,54]

The patient signed an informed consent form. An assessment of her general health status was undertaken, comprising medical anamnesis and physical examination including vital signs (blood pressure and pulse rate). Other preoperative procedures were examination of her oral mucosal status, impression taking to assess if enough space in the third molar region is available for the Crown placement, and radiographic assessment whether the bone structure (including inferior alveolar nerve location) is suitable for implantation. The patient was asked to rank her status in regard to a series of symptoms, using a scale ranging from 0 (worst) to 10 (best). She gave a mark of 2 to oral wetness, 1 to oral burning, 1 to quality of life, 4 to swallowing capacity, and 3 to speaking ability. In addition, she stated that she wakes up four times per night because of oral dryness

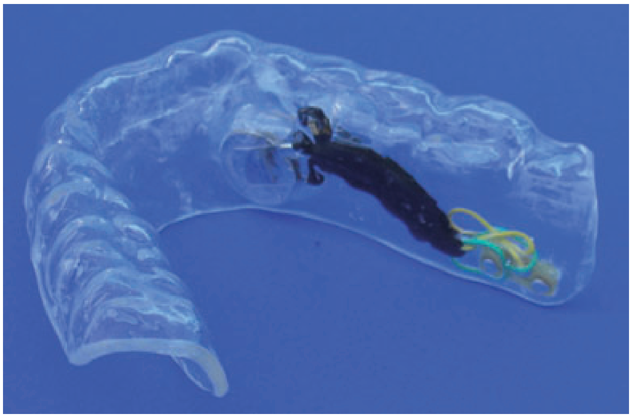

Figure 3 Saliwell GenNarino, the removable version of an electric stimulation device.

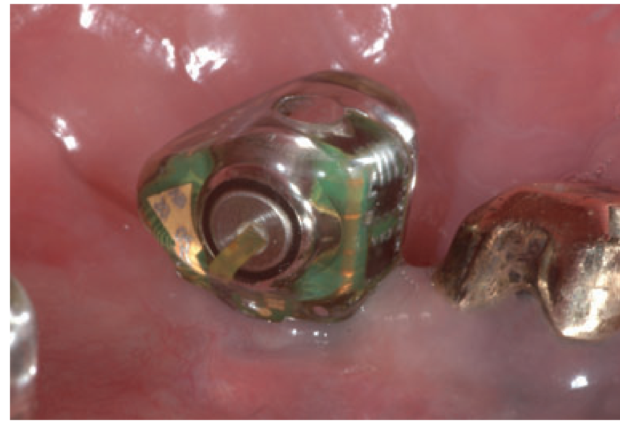

Figure 5 Buccal view of the device engaged to the implant. Note the relation to the telescopic infra structure.

and that she always feels her mouth to be dry and burning. A collection of saliva revealed a secretion rate of 0.021 mL/min (unstimulated) and 0.043 mL/min (stimulated). An implant was placed in the left lower edentulous area, distal to a posterior telescopic infra abutment, avoiding interference with the super structure, a telescopic removable partial denture. The implant (3.75 × 13 mms Brånemark System®, Nobel Biocare) was placed following the long axis of the bone in the area, taking advantage of the anatomic lingual inclination of the crest. After proper healing time (6 weeks), the Saliwell Crown was engaged (20 torque) to the implant by using an original implant-abutment screw. The device was activated with a dedicated remote control as presented above (Figures 3–8).

Ten days after the initiation of treatment and activation, the patient entered the clinic for symptoms assessment and salivary secretion tests. The results proved a marked symptomatic improvement. She ranked her oral wetness, 5; oral burning, 4; quality of life, 3; swallowing capacity, 5; and speaking ability, 5. She

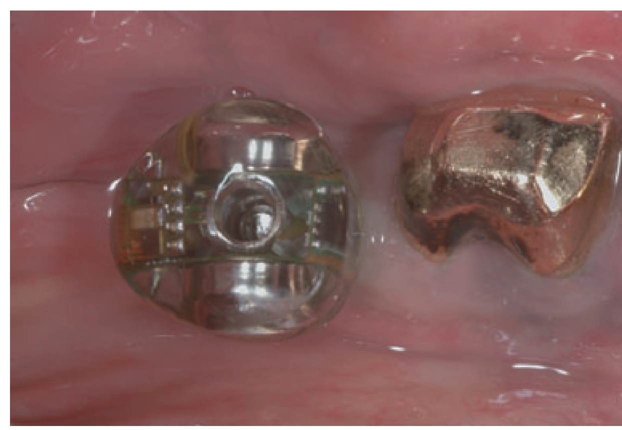

Figure 6 Occlusal view of the device presenting the screw hole. No sharp edges or elements exist.

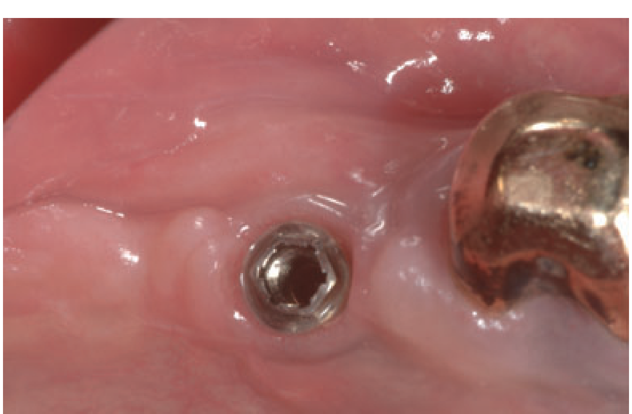

Figure 4 The implant site ready for the connection of the stimulation device. The implant was positioned lingually as close as possible to the lingual nerve to enhance stimulation.

Figure 7 Buccal view of the device presenting the telescopic removable partial denture in place. Note the lingual inclination of the device.

Figure 8 Lingual view of the device presenting the telescopic removable partial denture in place. Note the lingual inclination of the device.

reported that she wakes up three times per night because of oral dryness and that the frequency of dry and burning mouth has decreased. A collection of saliva disclosed a slight increase in the flow rate, which was 0.025 mL/min (unstimulated) and 0.064 mL/min (stimulated). The patient feedback was generally positive except for a complaint of several events of drooling.

After 1 year, the results were encouraging, following the patient's report on ease of dryness symptoms and a subjective increase in oral wetness, which was tested and confirmed clinically. She stated now that the degree of oral wetness is 6, of oral burning is 5, of quality of life is 5, of swallowing capacity is 7, and of speaking ability remained at 5. She reported that she wakes up once to three times per night because of oral dryness and that the frequency of dry and burning mouth continued to diminish. A collection of saliva disclosed a further increase in the flow rate to 0.043 mL/min (unstimulated) and to 0.069 mL/min (stimulated).

DISCUSSION

The treated patient was on polypharmacy therapy, including antihypertensives and tranquilizers. A recent study[55] reported that, compared with nonusers, users of cardiovascular agents, including antihypertensives display significant decreases in parotid stimulated and submandibular/sublingual unstimulated and stimulated salivary flow rates. Similar findings for tranquilizers regarding submandibular/sublingual output were obtained, but the diminished parotid secretion was the unstimulated one.

In the search for a practical relief of symptoms, an electronic stimulator was introduced to the US market in the late 1980s with promising results.[31] The major disadvantage was the inconvenience of use. The device presented in this report is small and convenient and may provide patients with xerostomia with a preferred solution for their dry mouth problem. The availability of bone for implantation is, of course, a core requisite, but the authors believe that short implants may serve especially for such cases as the device has no role in occlusal function.

Neural electrostimulation of salivary gland function by application of electrical current, through the oral mucosa, on afferent nerve pathways receptors has been reported to increase production of saliva and to reduce the symptoms of xerostomia in patients with dry mouth. It is believed that afferent nerves carry such impulses to the salivary nuclei (salivation center) in the medulla oblongata, which in turn directs signals to the efferent part of the reflex leading to initiation of salivation.[56] More recently, the use of extraoral transcutaneous electric nerve stimulation (TENS) over the parotid gland was reported to effectively increase saliva production in healthy individuals, suggesting that TENS might directly stimulate the auriculotemporal nerve that supplies secretomotor drive to the parotid gland.[57] Overall, there is enough evidence to say that electrical stimulation, either intraoral or extraoral, of nerves pertinent to salivary glands secretion control is able to increase salivary flow and oral wetness and decrease the symptoms of mouth dryness.

Because of the absence of negative side effects, electrostimulation theoretically overcomes the limitations of current xerostomia treatments and could represent a reasonable therapeutical option for patients with dry mouth. Saliwell Crown is a device aimed at implementing the salivary electrostimulation concept, realized in a miniaturized intraoral device mounted on a dental implant, capable of continuous autoregulated stimulation, and controlled by a remote control on demand. The transmission of the electrical current to the tissue is optimal because the electrodes of the device are in intimate contact with the sulcular epithelium surrounding the Saliwell Crown neck next to the interface with the implant.

The use of Saliwell Crown resulted in remarkable improvement of subjective parameters and in a more modest increase in salivary secretion. It is noteworthy that not only oral dryness symptoms, quality of life, and oral functional parameters (speech and swallowing) improved but also the oral burning sensation. Eliav and colleagues[58] found chorda tympani dysfunction in 82% of patients with burning mouth syndrome. Saliwell Crown is aimed at stimulating the chorda tympani through the lingual nerve stimulation. This may explain the improvement in burning sensation of the patient, although placebo effect cannot be ruled out, because of the well-recognized psychogenic component of burning mouth syndrome.[23]

Salivary flow assessment was performed by expectoration. This traditional salivary collection method does not assess the total fluid output, but rather the net output of saliva after loss of fluid by evaporation and/or by mucosal absorption.

Previous studies have demonstrated that assessment of the salivary film thickness covering oral surfaces might be a more appropriate method for diagnosing dry mouth, as it is a direct measurement of wetness of the mucosal tissues and identifies those who perceive dryness but are not considered to be hyposalivators because of resting salivary flow >0.1 to 0.2 mL/min. Collins and Dawes[59] calculated that, if saliva was evenly distributed throughout the mouth, it would present as a thin film of 72 to 100 μm thickness after and before swallowing, respectively, in interposition between two opposing surfaces of the mouth in contact. The film thickness values reported by Wolff and Kleinberg[60] are not very different, as they quote about 0.042 mm for normal salivators (which is half of the film shared by two opposing surface), while Collins and Dawes[59] quote 0.035 (after swallowing) and 0.050 m (before). According to Wolff and Kleinberg, the hard palate should be considered the primary site of dry-mouth perception, and the threshold for the perception of dryness is about 10 mm and below.

The thickness of the salivary film was not measured in the present patient, but it can be assumed that her subjective improvement is a result of thickening of the salivary film, which was manifested in a modest increase in the expectoration rate of saliva. From all that, one may learn that the key factor of xerostomia is salivary film thickness and not secretion rate. Patients with xerostomia do not present good correlation between the degree of complaint and unstimulated salivary flow rate. Small increases in salivary secretion, sufficient to render the salivary coating of oral mucosal surfaces thicker, may thus result in significant symptomatic improvement. Again, it must be stressed that those increases will not necessarily be reflected in enhanced saliva collections by expectoration.

In summary, the salivary glands of the studied xerostomic patient showed a good response to electrostimulation by the Saliwell Crown. This had a beneficial effect on the patient's subjective condition. Chronically applied electric stimulation lead to a cumulative effect, inducing constant and lasting salivation and significantly impacting the patient's quality of life.

Further scientific study and investigation are needed to confirm the preliminary clinical results.

CONCLUSIONS

- Within the limitation of this study, the Saliwell Crown presented promising good results, positively affecting the quality of life of a patient with xerostomia.
- No significant side effects, either local or systemic, were observed.
- Because of the intimate contact of the Crown electrodes with the tissue and the minimal energy waste (because electrodes are placed in a "closed" environment, which is the gingival sulcus), the performance (effect per energy unit) was optimized, allowing the use of little energy to reach a significant effect.
- The patient reported remarkable cumulative subjective improvement in oral and quality of life-related parameters, accompanied by a modest increase of salivary flow rate.
- The idea of the Saliwell GenNarino removable device was applied successfully into a crown-sized fixed appliance with promising results.

REFERENCES

1. Valdez IH, Fox PC. Interactions of the salivary and gastrointestinal systems. I. The role of saliva in digestion. Dig Dis 1991; 9:125–132.
2. Levine MJ, Aguirre A, Hatton MN, Tabak LA. Artificial salivas: present and future. J Dent Res 1987; 66:693–698.
3. Mandel ID. The functions of saliva. J Dent Res 1987; 66:628–632.
4. Fox PC, van der Ven PF, Sonies BC, Weiffenbach JM, Baum BJ. Xerostomia: evaluation of a symptom with increasing significance. J Am Dent Assoc 1985; 110:519–525.
5. Wolff A. Salivary gland disorders associated with autonomic dysfunction. In: Korczyn AD, ed. Handbook of autonomic nervous system dysfunction. New York: Marcel Dekker, 1995:293–309.

6. Seifert G. Diseases of the salivary glands. Stuttgart: Thieme, 1986.
7. Dawes C. Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. J Dent Res 1987; 66:648–653.
8. Garrett JR. The proper role of nerves in salivary secretion: a review. J Dent Res 1987; 66:387–397.
9. Emmelin N. Nerve interactions in salivary glands. J Dent Res 1987; 66:509–517.
10. Vissink A, Wolff A, Veerman E. Saliva collectors. In: Wong D, ed. Saliva diagnostics. Ames, IA: Wiley-Blackwell, 2008:37–59.
11. Eshel Y, Korczyn AD. Central connections of the salivation reflex in man. Exp Neurol 1987; 62:497–499.
12. Froehlich DA, Pangborn RM, Whitaker JR. The effect of oral stimulation on human parotid salivary flow rate and alpha-amylase secretion. Physiol Behav 1987; 41:209–217.
13. Anderson DJ, Hector MP. Periodontal mechanoreceptors and parotid secretion in animals and man. J Dent Res 1987; 66:518–523.
14. Baum BJ. Salivary gland fluid secretion during aging. J Am Geriatr Soc 1989; 37:453–458.
15. Izutsu KT. Physiological aspects of salivary gland function. Compend Contin Educ Dent 1989; 13:S450–S456.
16. Sreebny LM, Valdini A. Xerostomia. Part I: relationship to other oral symptoms and salivary gland hypofunction. Oral Surg Oral Med Oral Pathol 1988; 66:451–458.
17. Grisius MM. Salivary gland dysfunction: a review of systemic therapies. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001; 92:156–162.
18. Billings RJ. Xerostomia and associated factors in a community-dwelling adult population. Community Dent Oral Epidemiol 1996; 24:312–316.
19. Nederfors T, Isaksson R, Mörnstad H, Dahlöf C. Prevalence of perceived symptoms of dry mouth in an adult Swedish population – relation to age, sex and pharmacotherapy. Community Dent Oral Epidemiol 1997; 25:211–216.
20. Billings RJ. Saliva flow and dental caries in aging adults. In: Bowen WH, Tabak LA, eds. Cariology for the nineties. Rochester, NY: University of Rochester Press, 1993:235–247.
21. Sreebny LM, Valdini A. Xerostomia: a neglected symptom. Arch Intern Med 1987; 147:1333–1337.
22. Wolff A, Gadre A, Begleiter A, Moskona D, Cardash H. The correlation between patient satisfaction with complete dentures and parameters of denture quality, oral condition, and the flow rate of submandibular/sublingual salivary glands. Int J Prosthodont 2003; 16:45–48.
23. Pedersen AML, Smidt D, Nauntofte B, Christiani CJ, Jerlang BB. Burning mouth syndrome: etiopathogenic mechanisms, symptomatology, diagnosis and therapeutic approaches. Oral Biosci Med 2004; 1:3–19.
24. Astor FC, Hanft KL, Ciocon JO. Xerostomia: a prevalent condition in the elderly. Ear Nose Throat J 1999; 78:476–479.
25. Silvestre Donat FJ, Serrano Martinez C. Burning mouth syndrome: concepts review and update. Med Oral 1997; 2:30–38.
26. Atkinson JC, Travis WD, Pillemer SR, Wolff A, Fox PC. Major salivary gland function in primary Sjogren's syndrome and its relationship to clinical features. J Rheumatol 1990; 17:318–322.
27. Ship JA, DeCarli C, Friedland RP, Baum BJ. Diminished submandibular salivary flow in dementia of the Alzheimer type. J Gerontol 1990; 45:M61–M66.
28. Newrick PG, Bowman C, Green D, et al. Parotid salivary secretion in diabetic autonomic neuropathy. J Diabetes Complications 1991; 5:35–37.
29. Wolff A, Atkinson JC, Macynski AA, Fox PC. Pretherapy interventions to modify salivary dysfunction. Natl Cancer Inst Monogr 1990; 9:87–90.
30. Schubert MM, Izutsu KT. Iatrogenic causes of salivary gland dysfunction. J Dent Res 1987; 66:680–688.
31. Talal N. The clinical effects of electrostimulation on salivary function of Sjogren's syndrome patients. A placebo-controlled study. Rheumatol Int 1992; 12:43–45.
32. Sreebny LM. Saliva: its role in health and disease. Int Dent J 1992; 42:291–304.
33. Anderson LC, Garrett JR, Zhang X, Proctor GB, Shori DK. Differential secretion of proteins by rat submandibular acini and granular ducts on graded autonomic nerve stimulations. J Physiol (Lond) 1995; 485:503–511.
34. Calvert Heck PM, Edwards AV. Autonomic control of submandibular protein secretion in the anaesthetized calf. Exp Physiol 1998; 83:545–556.
35. Edwards AV, Garrett JR, Proctor GB. Secretory interactions between the sympathetic and parasympathetic innervations of the submandibular gland in the anaesthetized cat. Exp Physiol 1997; 82:697–708.
36. Izumi H, Kanita K. Low-frequency subthreshold sympathetic stimulation augments maximal reflex parasympathetic salivary secretion in cats. Am J Physiol 1995; 268:R1188–R1195.
37. Kyriacou K, Garrett JR, Gjöstrup P. Structural and functional studies of the effects of parasympathetic nerve stimulation on rabbit submandibular salivary glands. Arch Oral Biol 1986; 31:235–244.
38. Montastruc P, Berlan M, Montastruc JL. Effects of yohimbine on submaxillary salivation in dogs. Br J Pharmacol 1989; 98:101–104.
39. Nakahari T, Nakahari T, Miyamoto M, Yoshida H, Tanaka H, Imai Y. Continuous measurements of tissue impedance during secretion in dog submandibular gland. Jpn J Physiol 1988; 38:699–712.
40. Schneyer CA, Hall HD. Effects of varying frequency of sympathetic stimulation on chloride and amylase levels of saliva elicited from rat parotid gland with electrical stimulation of both autonomic nerves. Proc Soc Exp Biol Med 1991; 196:333–337.

41. Tobin G, Edwards AV, Bloom SR, Ekström J. Nitric oxide in the control of submandibular gland function in the anaesthetized ferret. Exp Physiol 1997; 82:825–836.
42. Yu JH. The influence of varying the electrical frequency of sympathetic nerve stimulation on fluid and calcium secretion of the rat parotid salivary gland. Arch Oral Biol 1990; 35:39–43.
43. Strietzel FP, Martín-Granizo R, Fedele S, et al. An electrostimulating device in the management of xerostomia. Oral Dis 2007; 13:206–213.
44. Kiesselbach JE, Chamberlain JG. Clinical and anatomic observations on the relationship of the lingual nerve to the mandibular third molar region. J Oral Maxillofac Surg 1984; 42:565.
45. Alling CC. Dysesthesia of the lingual and inferior alveolar nerves following third molar surgery. J Oral Maxillofac Surg 1986; 44:454–457.
46. Lafaurie G, Fedele S, Martín-Granizo López R, Wolff A, Strietzel FP, 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.
47. Pai S, Ghezzi EM, Ship JA. Development of a visual analogue scale questionnaire for subjective assessment of salivary dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001; 91:311–316.
48. Thomson WM, Chalmers JM, Spencer AJ, Williams SM. The Xerostomia Inventory: a multi-item approach to measuring dry mouth. Community Dent Health 1999; 16:12–17.
49. Nelson JF. Prevalence and significance of prescription medication usage among gerodontic patients. Gerodontology 1987; 6:17–22.
50. Handelman SL, Baric JM, Espeland MA, Berglund KL. Prevalence of drugs causing hyposalivation in an institutionalized geriatric population. Oral Surg Med Pathol 1986; 62:26–31.
51. Kreher JM, Graser GN, Handelman SL. The relationship of drug use to denture function and saliva flow rate in a geriatric population. J Prosthet Dent 1987; 57:631–638.
52. Persson RE, Izutsu KT, Treulove EL, Persson R. Differences in salivary flow rates in elderly subjects using xerostomic medications. Oral Surg Med Pathol 1991; 72:42–46.
53. Wolff A, Stahl B. Reference guide to xerogenic drugs in Israel. J Isr Dent Assoc 1999; 16:51–76.
54. Guijarro B. Treatment of xerostomia: a review. Med Oral 2001; 6:7–18.
55. Wolff A, Zuk-Paz L, Kaplan I. Major salivary gland output differs between users and nonusers of specific medication categories. Gerodontology 2008; 25(4):210–216.
56. Fedele S, Wolff A, Strietzel FP, Martıń-Granizo R, Porter SR, Konttinen YT. Neuro-electrostimulation in the treatment of hyposalivation and xerostomia in Sjögren’s syndrome: a salivary pacemaker. J Rheumatol 2008; 35:1489–1494.
57. 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; 99:316–320.
58. Eliav E, Kamran B, Schaham R, Czerninski R, Gracely RH, Benoliel R. Evidence of chorda tympani dysfunction in patients with burning mouth syndrome. J Am Dent Assoc 2007; 138:628–633.
59. Collins LMC, Dawes C. The surface area of the adult human mouth and thickness of the salivary film covering the teeth and oral mucosa. J Dent Res 1987; 66:1300–1302.
60. Wolff M, Kleinberg I. Oral mucosal wetness in hypo- and normosalivators. Arch Oral Biol 1998; 43:455–462.