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Efficacy and Safety of an Intraoral Electrostimulation Device for Xerostomia Relief

A Multicenter, Randomized Trial

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Objective. **To evaluate the efficacy and safety of an intraoral electrostimulation device, consisting of stimulating electrodes, an electronic circuit, and a power source, in treating xerostomia. The device delivers electrostimulation through the oral mucosa to the lingual nerve in order to enhance the salivary reflex.**

Methods. **The device was tested on a sample of patients with xerostomia due to Sjögren's syndrome and other sicca conditions in a 2-stage prospective, randomized, multicenter trial. Stage I was a double-blind, crossover stage designed to compare the effects of the electrically active device with the sham device, each used for 1 month, and stage II was a 3-month open-label stage designed to assess the long-term effects of the active device. Improvement in xerostomia severity from baseline was the primary outcome measure.**

Results. **A total of 114 patients were randomized. In stage I, the active device performed better than the**

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sham device for patient-reported xerostomia severity ($P < 0.002$), xerostomia frequency ($P < 0.05$), quality of life impairment ($P < 0.01$), and swallowing difficulty ($P < 0.02$). At the end of stage II, statistically significant improvements were verified for patient-reported xerostomia severity ($P < 0.0001$), xerostomia frequency ($P < 0.0001$), oral discomfort ($P < 0.001$), speech difficulty ($P < 0.02$), sleeping difficulty ($P < 0.001$), and resting salivary flow rate ($P < 0.01$).

Conclusion. **Our findings indicate that daily use of the device alleviated oral dryness, discomfort, and some complications of xerostomia, such as speech and sleeping difficulties, and increased salivary output. The results show a cumulative positive effect of the device over the period of the study, from baseline to the end of the trial.**

Xerostomia, i. e., the subjective sensation of dry mouth, is a hallmark of Sjögren's syndrome (SS). This symptom is frequently associated with difficulties in swallowing, speech, and sleeping. Xerostomia may indicate that salivary output is decreased, exposing patients to a higher risk of dental caries, periodontal diseases, and oral infections (1,2). Salivary secretion is regulated by an autonomic reflex arch. Afferent impulses induced by chemical (gustatory) stimulation, mechanical stimulation (such as chewing food, tactile perception of foreign bodies in the mouth, or mouth muscles, e. g., tongue movements), or electrical stimulation of the oral mucosa are carried to the solitary nucleus in the medulla via the facial (VII) and glossopharyngeal (IX) nerves. Stimuli coming from other areas of the body, such as smell and sight, are also integrated in the solitary nucleus. Efferent signals to the sublingual and submandibular glands are transmitted through the facial nerve via the submandibular ganglion and to the parotid glands through the glossopharyngeal nerve via the otic ganglion, leading to salivation (3–5).

Relief of xerostomia is achieved by increasing oral moisture using over-the-counter oral comfort agents or systemic sialagogues. Although safe, the former provide only transient alleviation, requiring frequent application. Systemic sialagogues are effective in the relief of xerostomia, but have potential systemic adverse effects (6). It would thus be desirable to have a therapeutic tool combining the efficacy of systemic sialagogues with the safety of local agents. Such a treatment could exploit the existence of the salivary reflex by stimulating it electrically rather than pharmacologically.

Recently, an electronic intraoral device was developed in the context of a European Union–funded R&D project (IST-2001-37409). It was tested on patients with xerostomia, with the assumption that it would enhance the salivary reflex. Those experiments, in which electrostimulation was delivered to the oral mucosa for 10 minutes, resulted in a significant decrease in oral dryness (7). The purpose of the present study was to test the efficacy and safety of the electrostimulation device in a long-term, prospective, multicenter trial. The primary end point was improvement of xerostomia, and the secondary ones were improvement of associated symptoms, increased salivary output, and the absence of adverse events.

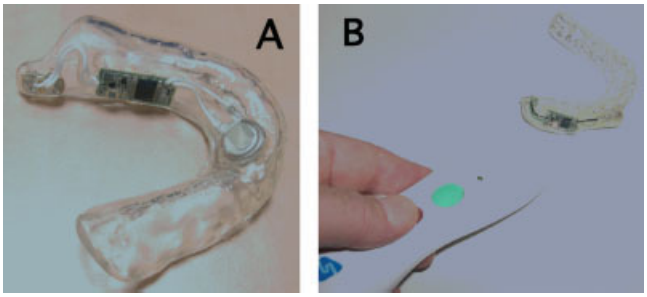

Figure 1. The intraoral electrostimulation device with the electronic circuit on the lingual side (**A**) and with the electronic circuit on the buccal side (**B**), switched on and off by the remote control.

PATIENTS AND METHODS

Device description. The intraoral electrostimulation device consists of a mouthpiece casted individually to fit the mandibular dental arch and an infrared remote control (Figure 1). It contains an electronic circuit (with a microprocessor and a receiver of remote control signals), a pair of stimulating electrodes, and a battery. The electrodes directly contact the oral mucosa in the mandibular third molar area, in proximity to the lingual nerve. Thus, no conductive gel is needed to convey electrostimulation to the tissue.

The patient activates and deactivates the electrical stimulation by pressing the "on" and "off" buttons of the remote control, respectively. The electrical current is of low intensity and is not felt by the patient. An amber light that blinks upon activation of the remote control ensures that the device is working as intended. Failure to blink means that the device is not functional and needs to be returned, and that a new one has to be ordered.

Study design. The study was conducted in full accordance with the World Medical Association Declaration of Helsinki and the additional ethics requirements of the countries where the research has been carried out. The study was approved by all ethics boards and registered at ClinicalTrials.gov (US National Institutes of Health; identifier NCT00509808), indicating an estimated target of 200 patients (in case the interim results required increasing the number of

subjects determined in the sample size calculation), with investigators of each center being asked to completely evaluate up to 10 patients. All study subjects provided written informed consent.

Xerostomia patients were recruited from the following 14 institutions in 13 countries: Charité Universitätsmedizin Berlin (Berlin, Germany), Hebrew University (Jerusalem, Israel), Hospital Clínico San Carlos (Madrid, Spain), Indiana University (Indianapolis, IN), Istanbul University (Istanbul, Turkey), Malmö University (Malmö, Sweden), McGill University (Montreal, Ontario, Canada), Universidad El Bosque (Bogotá, Colombia), Universidad Nacional Autónoma de México (UNAM; Mexico City, Mexico), Universidade de Brasilia (Brasilia, Brazil), Università di Palermo (Palermo, Italy), University of Helsinki (Helsinki, Finland), University of Kentucky (Lexington, KY), and University of Zagreb (Zagreb, Croatia). Patients with xerostomia due to SS and other conditions were eligible. SS patients were diagnosed by the referring or participating (in the study) rheumatologists using the American–European Consensus Group criteria (8). Standard codes for diagnosis were not used due to the variety of diagnoses that could be considered in the screening process. Excluded from the study were those younger than 18 years old; patients with human immunodeficiency virus, hepatitis C virus infection, or other severe diseases except for chronic graft-versus-host disease (GVHD); patients using anticoagulants, pacemakers, or defibrillators; patients with an allergy to the materials used in the electrostimulation device; patients with mental disease or depression; pregnant women; patients with chronic or recurrent, erosive or ulcerative, or premalignant or malignant oral lesions; patients with oral anatomic characteristics precluding the use of the device; and patients showing poor oral hygiene. Patients taking systemic sialagogues were asked to discontinue their medication for at least 7 days before commencement of the study and during the first 2 months of the trial. Their compliance was validated using questionnaires.

This prospective randomized crossover trial was divided into 2 stages. The first stage (stage I) aimed to determine whether electrostimulation has an additive effect on mechanical stimulation achieved by the device's foreign body effect in the mouth. The second stage (stage II) aimed to assess the long-term effects of the device on xerostomia parameters. During both stages, patients were instructed to use the device not more than once every hour but otherwise as many times as they liked every day.

In stage I, the electrostimulation device was used for 10 minutes at a time in either sham mode (mechanical stimulation) or active mode (mechanical and electrical stimulation), each for 1 month, in a double-blind manner. This time period was chosen since it was previously used in a preliminary proof-of-principle study, in which the device was used in a clinic for 10 minutes (7). The sequence of sham and active use was assigned randomly to each patient and was generated and managed centrally by the coordinating unit using the Microsoft Excel randomization tool. Randomization was neither blocked, due to the crossover study design, nor was it stratified, due to uncertainty about which patient characteristics might influence response to treatment. Identical-looking remote controls were assigned to each patient, with precoded software commands set for either not activating (sham) or activating (active) the electrical stimulation upon pressing the "on" button, in accordance with the randomization sequence. Each remote control was used in a randomly assigned order (first month or second month). The patients were blinded with regard to the type of stimulation (mechanical only or mechanical-electrical). The local investigators were also blinded with regard to the status of the randomization and performed the outcome assessment in a blinded manner. Patients received each remote control at the beginning of the month for which it should be used. Thus, the first remote control was collected before the second one was delivered.

Stage II was an open-label phase, during which only active devices were originally planned to be used for 9 months after the completion of stage I in order to assess the cumulative effect of electrostimulation from baseline, throughout the active month of stage I until the end of the study. At the beginning of the study, together with the stage I randomization, patients were also randomly allocated to use the device during stage II either 1, 5, or 10 minutes at a time. In the present study we analyzed the results of stage I and the first 3 months of stage II (hereinafter "stage II") for a total of 5 months of followup, in order to enable comparison of its findings to the findings of the few previous high-quality studies that have evaluated other therapies for xerostomia over 3–6 months (9–11).

Outcome measures. The devices were manufactured by the company that initiated the study, Saliwell Ltd., using impressions obtained from the patients' dental arches. Saliwell Ltd. provided the devices, but did not provide honoraria to the investigators or support to their local research infrastructure to perform the study. After baseline, when the device was delivered to the patients and stage I started, the clinical followup consisted of 3 outcome assessments: 1) the end of the first month, 2) the end of the second month and the beginning of stage II, and 3) the end of the fifth month. At each followup visit, questionnaires were administered, whole saliva was collected, and safety-related information was obtained. The primary outcome (severity of xerostomia) and patient-centered secondary outcomes were measured using a previously validated questionnaire (12,13). Answers to 5 questions were reported using 100-mm visual analog scales (VAS) running from the worst condition on the left end to the best on the right end of the line. Questions were: "How dry is your mouth today?" (dryness severity), "How comfortable is your mouth today?" (oral discomfort), "How do you rate your quality of life today?" (QOL), "How difficult is it for you to speak because of your dry mouth?" (speech difficulty), and "How difficult is it for you to swallow because of your dry mouth?" (swallowing difficulty). Two additional questions were: "How often does your mouth feel dry?" (dryness frequency, with the possible responses always, frequently, occasionally, and never, rated 1, 2, 3, and 4, respectively) and "During the past week, how many times on average did you wake up in the night due to dryness of your mouth?" (sleeping difficulty).

Other secondary outcome measures were resting and mastication-stimulated salivary flow rates, which were always assessed during morning hours. Patients were requested to take nothing into their mouths for 90 minutes or longer, and then to spit during 5 minutes into containers (catalog no. 25174; F. L. Medical), while avoiding swallowing. Salivary flow was stimulated by chewing a piece of Parafilm. Saliva volume

was determined gravimetrically (assuming a specific gravity of 1) (14).

As safety-related secondary outcome measures, vital signs, changes in health condition, and oral mucosal status were assessed. Any oral mucosal abnormality, e.g., discoloration, swelling, ulceration, or erosion, was recorded, as was any oral discomfort caused by the electrostimulation device and any device adjustment that consequently became necessary.

Statistical analysis. Based on previously reported reduction of xerostomia after 17 weeks of use of an antixerostomia agent (15), a sample size of 72 subjects was calculated to be necessary to detect a difference of 11 points on a VAS with an SD of 13 for a 2-sided test with 95% power and a 5% level of significance (16). The total number of subjects to be recruited was 110, assuming an attrition rate of 35%, which is to be expected in a long-term trial in which most subjects are elderly persons who are asked to repeatedly visit the clinic without monetary incentive.

Due to the absence of a washout period during stage I, the carryover effect was investigated using an analysis of variance for crossover design (17). The normality and equal variance assumptions were checked using the normal probability plot, residuals versus predicted, the Anderson-Darling test, and Levene's test (18).

For stage II analyses, the mixed model was used for analysis of variance with repeated measures to examine the time trend in each one of the outcome parameters. Several covariance structures were applied: compound symmetry, unstructured, and autoregressive. The most appropriate model was chosen according to Akaike's information criterion (19,20). Pairwise comparisons between periods of device use were conducted using Hochberg's adjustment method for multiple comparisons (21). Differences between the mucosal status in the patient subgroups were analyzed using chi-square and Wilcoxon tests. Parameters were compared between the patients with and those without SS at baseline, at the end of stage I, and at the end of stage II, using 2-sample *t*-tests. Patients who were diagnosed as having conditions other than SS were pooled together due to the small number of patients with each condition. Statistical associations between VAS scores and resting salivary flow rates were calculated using Spearman's rho. Due to the small number of subjects per center, the analyses were not adjusted for study center. Statistical analyses were performed by one of the authors (GRBM) and by the Statistics Unit of the Tel-Aviv Sourasky Medical Center, using SAS for Windows, version 9.1.3 (22).

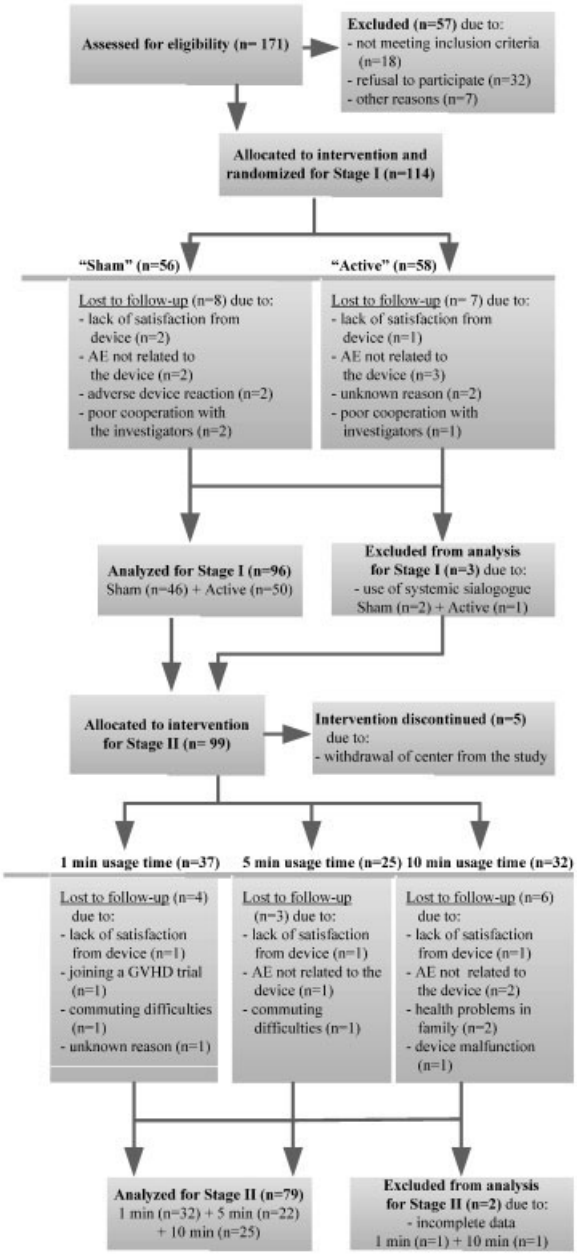

Figure 2. Disposition of the patients. AE = adverse event; GVHD = graft-versus-host disease.

RESULTS

Characteristics of the patients. As shown in Figure 2, after screening of 171 patients for eligibility, a total of 114 patients (intent-to-treat population) were evaluated and randomized between December 2006 and November 2009. Ninety-six patients (84%) completed stage I, and 79 patients (69%) completed stage II. Twenty-two patients were lost to followup due to lack of satisfaction with the electrostimulation device (n = 6), adverse events not related to device use (n = 8), familial problems (n = 2), joining a GVHD trial (n = 1), commuting difficulties (n = 2), or without explanation (n =3). The adverse events considered not to be related to device use were psychiatric/psychological problems (n = 2), general health deterioration (n = 1), stiffness of the neck as complication of radiotherapy (n = 1), pneumonia (n = 2), hospitalization due to

Table 1. Baseline characteristics of the patients with xerostomia*

		Diagnosis						Intervention		Followup status†		
	All patients (n = 114)	SS (n = 66)	Other than SS (n = 48)	Radio-therapy (n = 14)	Medi-cations (n = 9)	GVHD (n = 5)	Other or idiopathic (n = 20)	Sham (n = 56)	Active (n = 58)	Excluded from stage I (n = 18)	Excluded from stage II (n = 20)	Finished the study (n = 79)
% female	81	94	63	38	89	0	78	80	81	83	75	82
Age, years	60 ± 11	62 ± 10	57 ± 13	54 ± 11	61 ± 11	51 ± 17	58 ± 13	59 ± 12	60 ± 11	64 ± 11	55 ±15	60 ± 10
Diagnosis, % of patients												
SS	57	100	0	0	0	0	0	53	62	44	44	63
Radiotherapy	11	0	28	100	0	0	0	11	13	19	6	10
Medications	8	0	19	0	100	0	0	11	5	13	6	9
GVHD	4	0	9	0	0	100	0	2	5	0	17	1
Other or idiopathic	20	0	45	0	0	0	100	24	15	25	28	17
Dryness severity‡	34 ± 24	34 ± 23	34 ± 26	32 ± 28	41 ± 23	40 ± 25	31 ± 27	36 ± 26	32 ± 23	32 ± 25	30 ± 26	34 ± 24
Dryness frequency§	1.8 ± 0.7	1.8 ± 0.7	1.8 ± 0.7	1.6 ± 0.7	1.8 ± 0.7	1.5 ± 0.6	1.9 ± 0.8	1.9 ± 0.7	1.6 ± 0.7	1.8 ± 0.9	1.7 ± 0.8	1.7 ± 0.7
Discomfort‡	37 ± 25	39 ± 24	35 ± 27	31 ± 27	42 ± 27	24 ± 9	37 ± 29	38 ± 27	36 ± 23	34 ± 28	37 ± 29	37 ± 24
QOL‡	55 ± 24	54 ± 23	57 ± 25	49 ± 26	60 ± 23	77 ± 10	57 ± 26	55 ± 23	55 ± 25	53 ± 28	54 ± 24	56 ± 23
Speech difficulty‡	47 ± 28	42 ± 24	54 ± 32	46 ± 32	56 ± 33	80 ± 15	53 ± 32	48 ± 29	47 ± 28	46 ± 29	41 ± 33	49 ± 27
Swallowing difficulty‡	42 ± 30	36 ± 26	49 ± 34	25 ± 29	54 ± 33	69 ± 34	57 ± 32	42 ± 30	58 ± 38	37 ± 32	32 ± 34	44 ± 29
Wake up, times per night	1.9 ± 1.7	2.0 ± 1.8	1.8 ± 1.6	2.2 ± 1.8	2.2 ± 1.1	0.6 ± 1.3	1.7 ± 1.6	2.0 ± 1.9	1.8 ± 1.5	1.5 ±1.6	2.0 ± 2.1	2.0 ± 1.6
RSFR, μl/minute												
Mean ± SD	123 ± 155	108 ± 152	143 ± 159	35 ± 63	147 ± 175	164 ± 155	199 ± 168	146 ± 176	101 ± 129	76 ± 111	183 ± 224	116 ± 137
Median (range)	57 (0–748)	45 (0–748)	94 (0–639)	12 (0–230)	66 (0–480)	108 (48–392)	150 (0–639)	84 (0–748)	30 (0–508)	30 (0–380)	108 (0–748)	57 (0–550)
SSFR, μl/minute	452 ± 522	415 ± 545	502 ± 490	256 ± 426	463 ± 401	713 ± 511	624 ± 519	414 ± 437	488 ± 593	353 ± 462	434 ± 403	467 ± 557
Systolic BP, mm Hg	130 ± 19	132 ± 20	128 ± 17	125 ± 20	129 ± 10	115 ± 11	131 ± 17	131 ± 18	129 ± 20	133 ± 25	125 ± 13	131 ± 19
Diastolic BP, mm Hg	78 ± 12	77 ± 13	80 ± 11	77 ± 12	80 ± 9	75 ± 2	82 ± 11	78 ± 13	78 ± 11	79 ± 13	73 ± 12	80 ± 12
Heart rate	73 ± 9	73 ± 9	72 ± 10	72 ± 9	77 ± 8	65 ± 8	71 ± 10	73 ± 10	72 ± 9	69 ± 9	71 ± 10	74 ± 9
Oral mucosal changes, % of patients¶	14	6	22	8	25	100	15	16	12	7	27	12

* Except where indicated otherwise, values are the mean ± SD. Only the parameters speech difficulty and swallowing difficulty differed significantly between patients with Sjögren's syndrome (SS) and patients with all other diagnoses grouped together ($P < 0.05$). Only the parameters dryness frequency and swallowing difficulty differed significantly between patients in the sham intervention group and patients in the active intervention group ($P < 0.05$). There were no significant differences for any of the parameters between patients who were excluded from stage I, patients who were excluded from stage II, and patients who completed the study. GVHD = graft-versus-host disease; QOL = quality of life; RSFR = resting salivary flow rate; SSFR =stimulated salivary flow rate; BP = blood pressure.

† Three patients were excluded from the analysis for stage I (due to use of systemic sialagogues) but were still allocated to intervention in stage II.

‡ Scored on a visual analog scale ranging from 0 (worst) to 100 (best).

§ Scored on a scale of 1–4, where 1 = always, 2 = frequently, 3 = occasionally, and 4 = never.

¶ Percent of patients with ≥1 lesion.

arthritis (n = 1), and deterioration of GVHD (n = 1). Intervention was discontinued for 11 patients because of adverse device reaction (oral mucosal soreness [n = 2]), poor cooperation with the investigators (n = 3), device malfunction (n = 1), and withdrawal of centers from the trial (McGill University following the expiration of a funding grant [n = 1] and UNAM due to logistical difficulties [n = 4]). Due to the use of systemic sialagogues, 3 patients were excluded from the analysis in stage I, and 2 others were excluded from the overall analysis due to incomplete data.

Figure 2 shows that dropout occurred at random and was not related to the randomization assignment when subjects were lost to followup. The data in Table 1 show that patients who dropped out at any stage were not different from those who finished the study. The outcomes of stage I for those who completed this part of the study but dropped out later were similar to those for patients who completed the whole study (Table 2). There were not enough data on patients who dropped out before the end of stage I for outcome measures to be analyzed.

The baseline characteristics of the patients are displayed in Table 1. The mean age of participants was 60 years (range 19–78 years). As expected, the majority (81%) were women (23). Patients had xerostomia due to SS (57%), radiotherapy to the head and neck (11%), use of medications (8%), GVHD (4%), and other or idiopathic reasons (20%). The characteristics of the group of patients with xerostomia due to SS and the group of patients with xerostomia due to all other causes pooled together were similar, except for speech difficulty and swallowing difficulty, which were more severe in the SS group. The subgroups of patients with diagnoses other than SS displayed mostly similar baseline characteristics. However, the patients with xerostomia due to radiotherapy had lower salivary flow rates, and patients with GVHD had a higher rate of mucosal changes. Baseline characteristics were generally similar between the groups that were initially randomized to receive sham and active interventions in stage I, except for dryness frequency, which was worse in the active intervention group and swallowing difficulty, which was more severe in the sham intervention group. Resting salivary flow rate was positively and weakly correlated with the VAS scores at all 4 outcome assessments, as all ρ values were <0.45. Fourteen percent of the patients displayed oral mucosal changes; medication intake was registered in 79%, and 53% used xerogenic drugs.

The average daily cumulative length of use of the electrostimulation device was 40 minutes for stage I (e.g., use of the device 4 times per day for 10 minutes each time) and 21 minutes for stage II, ranging from 1 minute (e.g., 1 time per day for 1 minute each time) to 80 minutes (e.g., 8 times per day for 10 minutes each time). Throughout the study, the tested parameters were similar among patients with SS and all other patients pooled together.

Efficacy. In stage I, no significant carryover and sequence effects were found for any of the variables. Thus, the effects of the sham and active interventions were used for comparison regardless of their allocation schedule. The active intervention was superior to sham for the primary outcome measure (dryness severity; $P < 0.002$) (Figure 3). The active intervention also performed better than sham for some secondary outcome measures, either with statistical significance ($P < 0.05$ for dryness frequency, $P < 0.01$ for QOL, and $P < 0.02$ for swallowing difficulty), or with a tendency toward statistical significance ($P = 0.07$ for speech difficulty) (Table 2). No statistical significance was detected between the active and sham interventions for the parameters oral discomfort, sleeping difficulty, resting salivary flow rate, and stimulated salivary flow rate.

The length of use subgroups (1, 5, and 10 minutes) in stage II were pooled because no significant differences were detected between them for the tested variables, except for dryness frequency (for 1-minute use versus 5-minute use) and stimulated salivary flow rate (for 1-minute use versus 10-minute use) ($P < 0.05$ for both) (Table 2). From baseline until the end of stage II all parameters improved in the active intervention group, except for QOL, swallowing difficulty, and stimulated salivary flow rate. The primary outcome dryness severity ($P < 0.0001$) (Figure 3) and the secondary outcomes dryness frequency ($P < 0.0001$), oral discomfort ($P < 0.001$), speech difficulty ($P < 0.02$), sleeping difficulty ($P < 0.001$), and resting salivary flow rate ($P < 0.01$) all improved.

Improvements in the dryness severity and resting salivary flow rate parameters occurred in 70% and 63% of the participants, respectively. Nine patients started the study with a resting salivary flow rate and stimulated salivary flow rate of 0. In 7 of these patients, saliva could be collected at the end of stage II and dryness severity improved. Fifteen patients took a systemic sialagogue before joining the study. After the period of prohibition (stage I), one-third of them resumed taking those medications.

Safety. No significant changes in vital signs were detected. In 14% of the followup visits, patients reported a change in their health status, i.e., modification in

Table 2. Description of study outcome measures*

	Results for patients who completed stage I					Results for patients who completed stage II										
						Results at the end of stage II								Stage I results for patients who dropped out during stage II		
	Characteristics	Baseline	Sham	Active	P†	Characteristics	Baseline	End of "active" stage I	All lengths of usage pooled	P‡	1-minute use§	5-minute use§	10-minute use§	Characteristics	Sham	Active
Number of patients	96	–	–	–	NA	79	–	–	–	NA	32	22	25	21	–	–
% female	80	–	–	–	NA	82	–	–	–	NA	91	77	76	76	–	–
Age, mean ± SD	58.8 ± 11	–	–	–	NA	60 ± 10	–	–	–	NA	59 ± 12	59 ± 9	62 ± 8	55 ± 14	–	–
Diagnosis, % of patients																
SS	60.5	–	–	–	NA	63	–	–	–	NA	75	50	60	48	–	–
Radiotherapy	9	–	–	–	NA	10	–	–	–	NA	6	14	12	4.5	–	–
Medications	7	–	–	–	NA	9	–	–	–	NA	9.5	9	8	4.5	–	–
GVHD	4	–	–	–	NA	1	–	–	–	NA	0	0	4	14	–	–
Other or idiopathic	19.5	–	–	–	NA	17	–	–	–	NA	9.5	27	16	29	–	–
Dryness severity¶	–	34 ± 24	40 ± 24	43 ± 2	<0.002	–	34 ± 24	43 ± 23	47 ± 24	<0.0001	49 ± 29	46 ± 24	40 ± 27	–	34 ± 25	42 ± 20
Dryness frequency#	–	1.7 ± 0.7	1.9 ± 0.7	2.0 ± 0.7	<0.05	–	1.7 ± 0.7	2.0 ± 0.6	2.1 ± 0.7	<0.0001	2.4 ± 0.6	1.9 ± 0.7	2.0 ± 0.7	–	1.8 ± 0.6	2.1 ± 0.9
Discomfort	–	38 ± 25	40 ± 23	42 ± 21	NS	–	37 ± 24	42 ± 22	46 ± 24	<0.001	52 ± 28	45 ± 24	43 ± 26	–	33 ± 26	39 ± 21
QOL¶	–	56 ± 23	50 ± 24	54 ± 22	<0.01	–	56 ± 23	54 ± 23	55 ± 23	NS	59 ± 23	54 ± 24	54 ± 24	–	47 ± 25	56 ± 23
Speech difficulty¶	–	47 ± 28	49 ± 28	53 ± 26	0.07	–	49 ± 27	53 ± 26	56 ± 27	<0.02	62 ± 28	54 ± 30	58 ± 25	–	42 ± 27	52 ± 22
Swallowing difficulty¶	–	43 ± 30	44 ± 27	48 ± 26	<0.02	–	44 ± 29	48 ± 28	49 ± 27	NS	55 ± 27	47 ± 29	47 ± 30	–	45 ± 27	51 ± 26
Wake up, times per night	–	2.0 ± 1.7	1.9 ± 1.7	1.7 ± 1.6	NS	–	2.0 ± 1.6	1.7 ± 1.3	1.4 ± 1.3	<0.001	1.4 ± 1.4	1.0 ± 1.2	1.1 ± 1.4	–	2.5 ± 2.7	1.9 ± 2.6
RSFR, μl/minute	–	132 ± 161	123 ± 144	134 ± 155	NS	–	116 ± 137	130 ± 157	162 ± 187	<0.01	166 ± 170	179 ± 209	136 ± 196	–	138 ± 145	150 ± 147
SSFR, μl/minute	–	470 ± 532	415 ± 545	520 ± 602	NS	–	467 ± 557	522 ± 634	527 ± 649	NS	773 ± 798	417 ± 550	335 ± 416	–	428 ± 378	506 ± 443
Systolic BP, mm Hg	–	130 ± 18	126 ± 17	126 ± 18	NS	–	131 ± 19	129 ± 19	127 ± 16	NS	130 ± 18	123 ± 13	127 ± 18	–	122 ± 18	121 ± 14
Diastolic BP, mm Hg	–	78 ± 12	78 ± 11	77 ± 11	NS	–	80 ± 12	78 ± 11	77 ± 14	NS	79 ± 11	78 ± 9	74 ± 19	–	76 ± 10	76 ± 7
Heart rate	–	73 ± 9	74 ± 11	71 ± 12	NS	–	74 ± 9	72 ± 10	72 ± 12	NS	71 ± 16	74 ± 9	72 ± 8	–	71 ± 10	69 ± 19
Oral mucosal changes, % of patients**	–	14	15	16	NS	–	12	11	10	NS	4	9	18	–	15	16

* NA = not applicable; NS = not significant. See Table 1 for other definitions.
† Effect on baseline status of active versus sham interventions. The 95% confidence intervals (95% CIs) for the observed baseline means of the variables that were significantly different were −3.7, 5.6 for the sham intervention and 4.2, 13.7 for the active intervention for dryness severity; −0.03, 0.27 for the sham intervention and 0.09, 0.38 for the active intervention for dryness frequency; −9.5, −0.5 for the sham intervention and −5.1, 3.2 for the active intervention for QOL; and −3.5, 6.8 for the sham intervention and 1.2, 10.9 for the active intervention for swallowing difficulty.
‡ Time trend from baseline. The 95% CIs for the means of the variables that were significantly different were 29, 40 for baseline, 37, 48 for the end of the active month of stage I, and 42, 53 for the end of stage II for dryness severity; 1.6, 1.9 for baseline, 1.9, 2.2 for the end of the active month of stage I, and 2.0, 2.3 for the end of stage II for dryness frequency; 32, 43 for baseline, 37, 47 for the end of the active month of stage I, and 41, 52 for the end of stage II for discomfort; 43, 55 for baseline, 47, 59 for the end of the active month of stage I, and 50, 62 for the end of stage II for speech difficulty; 1.6, 2.4 for baseline, 1.4, 2.0 for the end of the active month of stage I, and 1.1, 1.7 for the end of stage II for wake up; and 85, 147 for baseline, 94, 166 for the end of the active month of stage I, and 120, 204 for the end of stage II for RSFR.
§ The only significant differences among the time of use groups were for dryness frequency (between the 1-minute use and 5-minute use groups) and SSFR (between the 1-minute use group and the 10-minute use group) ($P < 0.05$ for both comparisons).
¶ Scored on a visual analog scale ranging from 0 (worst) to 100 (best).
# Scored on a scale of 1-4, where 1 = always, 2 = frequently, 3 = occasionally, and 4 = never.
** Percent of patients with ≥1 lesion.

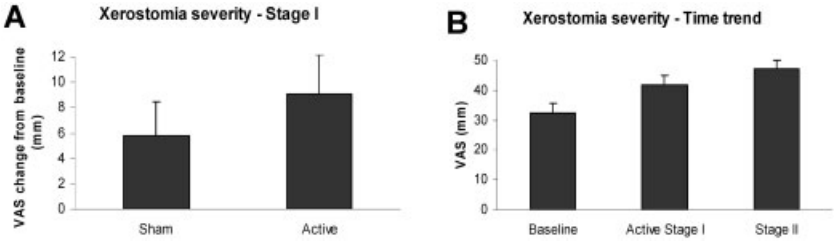

Figure 3. Severity of xerostomia, the primary outcome. **A**, Response to treatment, measured by change in visual analog scale (VAS) from baseline to the end of stage I. The sham intervention consisted of mechanical stimulation with the device, and the active intervention consisted of mechanical and electrical stimuli together. There was a significant difference between the sham and active interventions ($P < 0.002$). The 95% confidence intervals (95% CIs) observed for the sham and active groups were −3.7, 5.6 and 4.2, 13.7 mm, respectively. Bars show the mean ± SEM (n = 96 patients). **B**, VAS scores at baseline, at the end of stage I, and at the end of stage II. Bars show the mean ± SEM (n = 79). There was a significant difference in scores over time (P for trend < 0.0001). The 95% CIs for baseline, the end of the active month of stage I, and the end of stage II were 29, 40; 37, 48; and 42, 53 mm, respectively.

medication (52%), diagnosis of a new disease (45%), and surgery (3%), none of which were linked to the study.

In 34 (14%) of 246 followup visits, an oral mucosal finding was recorded. In 4 patients (all with GVHD) lichenoid changes, which are characteristic of the condition, were already present before the receipt of the electrostimulation device, and persisted throughout the study. All other lesions were mild, and were described as erythema, and as aphtha in one case. Oral mucosal lesions that could be related to the use of the device (because adjustment of the device yielded resolution of the lesions) were observed in 27% of the patients, mostly at one followup visit.

DISCUSSION

The primary study end point (improvement in the severity of xerostomia) and the secondary ones (improvements in the other symptoms, increased salivary output, and event-free use) were fully met in the present investigation. Electrostimulation delivered by the activated device had an additive effect to mechanical stimulation by the sham device for the parameters dryness severity ($P < 0.002$), dryness frequency ($P < 0.05$), QOL ($P < 0.01$), and swallowing difficulty ($P < 0.02$) and was not inferior to the sham device for any of the other parameters. During both stages of the study, the conditions that improved significantly during use of the activated device were dryness severity ($P < 0.0001$), dryness frequency ($P < 0.0001$), oral discomfort ($P < 0.001$), speech difficulty ($P < 0.02$), sleeping difficulty ($P < 0.001$), and resting salivary flow rate ($P < 0.01$). No worsening of the other parameters was observed (Table 2).

The finding that the differences between the active and sham interventions were free of carryover and sequence effects validated the study design, which did not include a washout period. The blindedness of the trial was ensured by the absence of any sensation upon electrostimulation, the use of the same device for the active and sham interventions, and the identical-looking activating and nonactivating remote controls.

In the present study, the symptom profile of the patients with SS was similar to that of all other patients, i.e, the symptoms and consequences of oral sicca were similar in all patients with xerostomia. Treatment of xerostomia is mainly symptomatic and nonspecific, with the same therapeutic agents being applied in all cases (24). Therefore, the efficacy of a xerostomia treatment is best evaluated by questionnaire (25). As in previous studies (10,11), salivary flow rates were used as secondary outcome measures since no gold standard regarding a flow rate value that distinguishes between normal and abnormal currently exists (26). Moreover, the results of the present study confirm the poor relationship between the xerostomia-related symptom profile and whole salivary flow rate. However, it has been suggested that minor gland saliva, which is poorly reflected in whole salivary flow rate, might affect subjective feelings of dry mouth (26). Thus, minor salivary flow rate may be

Table 3. Comparison between the present trial and previous studies that used systemic sialagogues in patients with xerostomia

Author, year (ref.)	Agent	Duration, months	No. of patients	Dropout rate, %	Underlying diagnoses	Xerostomia severity, % responders	Resting salivary flow rate, % responders	Patients with adverse effects, %	Types of adverse effects
Fox et al, 1991 (9)	Pilocarpine, 5 mg three times daily	6	39	21	Diverse	84*	67†	84	Systemic (sweating, sensation of warmth or flushing, urgency of urination)
Vivino et al, 1999 (10)	Pilocarpine, 5 mg four times daily	3	373	13	Sjögren's syndrome	61	Not mentioned	51	Systemic (sweating, urinary frequency, flushing)
Petrone et al, 2002 (11)	Cevimeline, 30 mg three times daily	3	197	18	Sjögren's syndrome	66	Not mentioned	48	Systemic (headache, sweating, abdominal pain, nausea, sinusitis, diarrhea, pharyngitis)
Present study	Electrostimulation	5	114	16 (in each stage)	Diverse	70*	63*	27	Local (oral mucosal lesions)

* Assessed at study end, compared to study baseline measurements.
† Assessed at followup visits, where posttreatment measurements were compared to pretreatment (visits' baseline) measurements.

assessed in future studies in order to investigate whether the function of those glands might be influenced by activity of the electrostimulation device.

The present results were compared with those of similarly designed high-quality studies (9–11) that were included in two recent systematic reviews (24,27). In Table 3, comparisons are drawn for xerostomia severity, as a primary outcome measure, and for resting salivary flow rate, since resting saliva is experienced by individuals for most of the day (28). The table shows that, although of similar efficacy, the intraoral electrostimulation device appears to be safer than approved medications to treat xerostomia, as the latter frequently cause systemic side effects. Such effects may also jeopardize the double-blind protocol of drug studies. In contrast, long-term use of the device resulted only in local, mild, and transient adverse events unrelated to its active ingredient, i.e., electrostimulation.

As in the studies to which the present one is compared (9–11), a potential limitation of the trial is the occurrence of missing data, which is inevitable in this particular clinical context. Fortunately, statistical analyses suggest that this did not result in any systematic bias. It is recognized that some of these cases may be outcome related, such as for patients who dropped out due to lack of satisfaction with the electrostimulation device, dropped out without explanation, or used systemic sialagogues. The risk of missing data in this study was anticipated due to the long duration of the trial, the advanced age of the patients, the lack of payment offered to them, and the nature of the condition that was treated, i.e., xerostomia, although a debilitating disorder, has no fatal consequences. A strategy aimed at handling missing data has been devised, including investigation of the pattern of missing data in previous trials on similar indications for related medicinal products (9–11), augmenting the required sample size by 35%, and statistically modeling the data. In future research, investigators will have to consider increasing the sample size to allow for stratification according to the duration of the xerostomia disorder before enrollment, since it would be reasonable to think that structurally less affected glands in early disease would be likely to respond better to the electrostimulation device.

The lack of improvement in self-assessed overall QOL, as opposed to all other parameters, could be explained by the impact on QOL of confounding factors other than xerostomia, such as keratoconjunctivitis sicca in SS (23), other comorbidities common in the elderly, and cancer- and treatment-related complications among the patients who underwent radiation (29). The smaller decline of QOL in the active intervention group is consistent with the direction of findings observed for other outcomes.

Electrostimulation applied on afferent pathways through the oral mucosa or on the skin covering the salivary glands has previously been shown to increase salivary production and relieve xerostomia in patients with SS and patients who had received radiotherapy (29–32). The electrodes of the device are placed in proximity to the lingual nerve (33). Thus, the salivary reflex is likely evoked through the excitation of (a) somatic afferent A beta fibers of the trigeminal nerve innervating oral mucous membranes and (b) visceral afferent fibers from the tongue and efferent secretomotor fibers innervating the submandibular and sublingual salivary glands, all relayed from, and to, the facial nerve via the chorda tympani (34–36).

The distance between the nerves and the stimulating electrodes is an important factor in the excitation provoked by an electrical current (36). When the device is manufactured, the electrodes are placed close to the

estimated location of the lingual nerve, but the actual distance may vary from 1 to 4 mm (33), limiting the predictability of the strength of the stimulating effect. In contrast, the results of this study suggest that the duration of stimulation may play a negligible role in the response potency.

It has been postulated that electrostimulation augments normal physiologic salivary reflexes (30). A study of the effect of transcutaneous nerve stimulation on radiotherapy-induced xerostomia demonstrated an increase in citric acid–primed salivary production lasting longer than the length of treatment delivery (29). Thus, it is hypothesized that long-term administration of electrostimulation could lead to resetting of the salivary reflex, which would become more responsive to all kinds of stimuli besides electrostimulation. In addition, stimulation of the salivary reflex arch might increase the release of nonadrenergic, noncholinergic trophic mediators and antiapoptotic stimuli, which might have long-term trophic effects on salivary gland parenchyma, leading to the regeneration of functional tissue (37–39). This assumption is based on studies that have demonstrated mitogenic responses in rat parotid and submandibular glands following electrical stimulation of their parasympathetic nerves (5).

Our results showed that the positive outcome obtained with the electrostimulated device was due to a cumulative effect over the period of the trial. Given the progressive nature of xerostomia, no improvement in patients' symptoms and clinical signs may be anticipated without intervention (40–42). Moreover, an eventual placebo effect is not sustained over time, as has been suggested in previous studies (43). Therefore, it seems that a prolonged treatment course with electrostimulation (e.g., at least 2 months) is to be recommended.

The improvement observed among patients who started the study with no collectable saliva is notable. It would be expected that a stimulatory device would only be effective for those patients demonstrating residual salivary gland function. However, as illustrated here, the absence of spitted saliva does not necessarily mean that salivary glands have ceased functioning completely. In summary, the intraoral electrostimulation device appears to be a physiologically sound, beneficial, and safe therapeutic option for the alleviation of xerostomia.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Wolff had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Sreebny LM, Valdini A. Xerostomia: a neglected symptom. Arch Intern Med 1987;147:1333–7.
2. Tabak LA, Levine MJ, Mandel ID, Ellison SA. Role of salivary mucins in the protection of the oral cavity. J Oral Pathol 1982;11: 1–17.
3. Pedersen AM, Bardow A, Beier Jensen S, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. Oral Dis 2002;8:117–29.
4. Steller M, Chou L, Daniels TE. Electrical stimulation of salivary flow in patients with Sjögren's syndrome. J Dent Res 1988;67: 1334–7.
5. Proctor GB, Carpenter GH. Regulation of salivary gland function by autonomic nerves. Auton Neurosci 2007;133:3–18.
6. Thelin WR, Brennan MT, Lockhart PB, Singh ML, Fox PC, Papas AS, et al. The oral mucosa as a therapeutic target for xerostomia. Oral Dis 2008;14:683–9.
7. Strietzel FP, Martin-Granizo R, Fedele S, Lo Russo L, Mignogna M, Reichart PA, et al. Electrostimulating device in the management of xerostomia. Oral Dis 2007;13:206–13.
8. Vitali CS, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al, and the European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
9. Fox PC, Atkinson JC, Macynski AA, Wolff A, Kung DS, Valdez IH, et al. Pilocarpine treatment of salivary gland hypofunction and dry mouth (xerostomia). Arch Intern Med 1991;151:1149–52.
10. Vivino FB, Al-Hashimi I, Khan Z, LeVeque FG, Salisbury PL III, Tran-Johnson TK, et al, for the P92-01 Study Group. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren's syndrome. Arch Intern Med 1999;159: 174–81.
11. Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum 2002;46:748–54.
12. Pai S, Ghezzi E, Ship J. Development of a Visual Analogue Scale

questionnaire for subjective assessment of salivary dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91: 311–6.
13. Thomson WM, Chalmers JM, Spencer AJ, Williams SM. The xerostomia inventory: a multi-item approach to measuring dry mouth. Community Dent Health 1999;16:12–7.
14. Vissink A, Wolff A, Veerman ECI. Saliva collectors. In: Wong DT, editor. Salivary diagnostics. Ames (IA): Wiley-Blackwell; 2008. p. 37–59.
15. Fox PC, Cummins MJ, Cummins JM. Use of orally administered anhydrous crystalline maltose for relief of dry mouth. J Altern Complement Med 2001;7:33–43.
16. Pocock SJ. Clinical trials: a practical approach. Chichester (UK): John Wiley & Sons, 1983.
17. Milliken GA, Johnson DE. Analysis of messy data. Vol. I: Designed experiments. 2nd ed. Boca Raton (FL): Chapman & Hall; 2009. p. 599–609.
18. Senn S. Cross-over trials in clinical research. 2nd ed. Chichester (UK): John Wiley & Sons; 2002.
19. Brown H, Prescott R. Applied mixed models in medicine. New York: John Wiley & Sons; 1999.
20. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974;AC-19:716–23.
21. Hochberg Y. Some conservative generalizations of the T-method in simultaneous inference. J Multivariate Anal 1974;4:224–34.
22. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS system for mixed models. Cary (NC): SAS Institute; 1996.
23. Jonsson R, Haga HJ, Gordon T. Sjögren's syndrome. In: Koopman WJ, editor. Arthritis and allied conditions: a textbook of rheumatology. 14th ed. Philadelphia: Lippincott Williams &Wilkins; 2001. p. 1736–8.
24. Brennan MT, Shariff G, Lockhart PB, Fox PC. Treatment of xerostomia: a systematic review of therapeutic trials. Dent Clin North Am 2002;46:847–56.
25. Thomson WM. Issues in the epidemiological investigation of dry mouth. Gerodontology 2005;22:65–76.
26. Eliasson L, Birkhed D, Carlen A. Feeling of dry mouth in relation to whole and minor gland saliva secretion rate. Arch Oral Biol 2009;54:263–7.
27. Von Bultzingslowen I, Sollecito TP, Fox PC, Daniels T, Jonsson R, Lockhart PB, et al. Salivary dysfunction associated with systemic diseases: systematic review and clinical management recommendations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103 Suppl:S57.e1–15.
28. Dawes C. Circadian rhythms in human salivary flow rate and composition. J Physiol 1972;220:529–45.
29. Wong RK, Jones GW, Sagar SM, Fargas-Babjak A, Whelan T. A Phase I-II study in the use of acupuncture-like transcutaneous nerve stimulation in the treatment of radiation-induced xerostomia in head-and-neck cancer patients treated with radical radiotherapy. Int J Radiat Oncol Biol Phys 2003;57:472–80.
30. Talal N, Quinn JH, Daniels TE. The clinical effects of electrostimulation on salivary function of Sjögren's syndrome patients: a placebo controlled study. Rheumatol Int 1992;12:43–5.
31. Hargitai IA, Sherman RG, Strother JM. The effects of electrostimulation on parotid saliva flow: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:316–20.
32. Domingo DL. The effects of electrostimulation on saliva production in postradiation head and neck cancer patients [abstract]. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:464.
33. 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;42:565–7
34. Pittman DW, Contreras RJ. Responses of single lingual nerve fibers to thermal and chemical stimulation. Brain Res 1998;790: 224–35.
35. Eliav E, Gracely RC. Sensory changes in the territory of the lingual and inferior alveolar nerves following lower third molar extraction. Pain 1998;77:191–9.
36. Fall M, Lindstrom S. Functional electrical stimulation: physiological basis and clinical principles. Int Urogynecol J 1994;5:296–304.
37. Mansson B, Nilsson BO, Ekstrom J. Effects of repeated infusions of substance P and vasoactive intestinal peptide on the weights of salivary glands subjected to atrophying influences in rats. Br J Pharmacol 1990;101:853–8.
38. Ekstrom J, Reinhold AC. Influence of parasympathetic non-adrenergic, non-cholinergic mechanisms on [^{3}H]thymidine uptake in rat parotid salivary glands in response to mastication following upon a liquid regimen. Arch Oral Biol 2001;46:1151–5.
39. Calafat M, Larocca L, Roca V, Hauk V, Pregi N, Nesse A, et al. Vasoactive intestinal peptide inhibits TNF-α-induced apoptotic events in acinar cells from nonobese diabetic mice submandibular glands. Arthritis Res Ther 2009;11:R53.
40. Thomson WM, Chalmers JM, Spencer AJ, Slade GD, Carter KD. A longitudinal study of medication exposure and xerostomia among older people. Gerodontology 2006;23:205–13.
41. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer 2010;18:1039–60.
42. Moutsopoulos HM. Sjögren's syndrome. In: Schumacher HR, Klippel JH, Koopman WJ, editors. Primer on the rheumatic diseases. 10th ed. Atlanta: Arthritis Foundation; 1993. p. 131–5.
43. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect. J Neurosci 2005;25:10390–402.