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Artigo Original

Transcutaneous Electrical Nerve Stimulation (TENS) on hyposalivation induced by radiotherapy in the head and neck region: a preliminary study

Efeito agudo da Transcutaneous Electric Nerve Stimulation (TENS) sobre a hipossalivação induzida pela radioterapia na região de cabeça e pescoço: um estudo preliminar

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Keywords

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ABSTRACT

Purpose: To verify the acute effect of electrostimulation on the salivary flow of patients with hyposalivation. **Methods:** Uncontrolled clinical trial evaluating 15 patients with hyposalivation induced by radiotherapy (RT) used for head and neck cancer treatment. Mean age of the patients was 56.8 ± 6.46 years. Males outnumbered females (73%). Transcutaneous Electrical Nerve Stimulation (TENS) was adjusted with 50Hz of frequency and 250μs of pulse width. Intensity was adjusted over a 20-minute period according to maximum tolerance. The electrodes were attached bilaterally on the region of the salivary glands. Evaluation of the salivary flow was performed through sialometry before and immediately after application of TENS. **Results:** The most prevalent region for RT was the oropharynx (80.0% of cases). The mean dose used in RT was 64.6 ± 7.27 Gy. After TENS, salivary flow increased significantly (p = 0.0051) from 0.05 (0.00; 0.40) mL/min to 0.10 (0.07: 0.40) mL/min. The response to TENS was directly correlated with the intensity of the tolerated electric current (r = 0.553; p = 0.032) and the dose used in RT (r = -0.514; p = 0.050). **Conclusion:** TENS was able to increase the salivary flow rate of patients with RT-induced hyposalivation.

Descritores

Transcutaneous Electric Nerve Stimulation
Saliva
Xerostomia
Neoplasias de Cabeça e Pescoço
Radioterapia

RESUMO

Objetivo: Verificar o efeito agudo da eletroestimulação sobre o fluxo salivar de pacientes com hipossalivação. **Método:** Ensaio clínico não controlado que avaliou o efeito de uma única aplicação da *Transcutaneous Electrical Nerve Stimulation* (TENS) sobre o fluxo salivar de 15 pacientes com hipossalivação induzida por radioterapia (RT), utilizada no tratamento de câncer de cabeça e pescoço. A média de idade dos pacientes foi de 56,8 ± 6,46 anos e o gênero masculino foi predominante (73%). A TENS foi programada com 50Hz de frequência, 250μs de largura de pulso e a intensidade foi ajustada ao longo dos 20 minutos conforme máxima tolerância. Os eletrodos foram fixados bilateralmente sobre a região das glândulas salivares. A avaliação do fluxo salivar foi realizada por meio de sialometria estimulada, antes e imediatamente após a aplicação da TENS. **Resultados:** Em 80% dos casos, o tratamento oncológico incluiu quimioterapia. A RT foi aplicada em 80% dos casos na região e orofaringe, com intensidade média de 64,6 ± 7,27 Gy. Após a TENS, o fluxo salivar aumentou significativamente (p = 0,0051), passando de 0,05 (0,00; 0,40) mL/min para 0,10 (0,07;0,40) mL/min. A resposta à TENS foi diretamente correlacionada à intensidade da corrente elétrica tolerada (r = 0,553; p = 0,032) e à dose utilizada na RT (r = -0,514; p = 0,050). **Conclusão:** A TENS aumentou significativamente o fluxo salivar de pacientes com hipossalivação induzida pela RT.

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INTRODUCTION

Head and neck cancer has an approximate incidence of 900,000 cases per year worldwide. In Brazil, according to estimates, 38,000 cases are expected in the biennium 2016-2017[1], hence it is considered as one of the most prevalent types of cancer[2].

There are different therapeutic options depending on the anatomical location of the tumor, histological type, extent of primary lesion, cervical lymphadenopathy, morbidity which is expected and associated with each modality of treatment, clinical condition and patient option. One of the main alternatives is surgical resection, associated or not with chemotherapy (CT) and radiotherapy (RT)[3].

RT destroys neoplastic cells by means of ionizing radiation, but it causes damage to surrounding cells[4]. Commonly, RT for head and neck tumors involves doses between 50-70 Gy, and adverse effects depend on the method in use, number of doses, intensity of exposure and individual characteristics. The main changes caused by the treatment are dysphagia, dysgeusia, mucositis, odynophagia, trismus, radiodermatitis and hyposalivation[5].

In general, radiation-induced hyposalivation occurs early. It starts in the second week of treatment, and it may interfere in phonation, mastication and deglutition abilities. Moreover, it increases the prevalence of infections such as candidiasis, dental caries and periodontal disease, thus significantly compromising the quality of life of patients[6].

There are several techniques for stimulation of salivary flow. Generally, they include mechanical approaches, medicaments, taste stimuli and electrical stimulation of the salivary glands[7]. However, many of the available techniques have limitations, important adverse effects and contraindications[8].

Although salivary substitutes are frequently used and are effective at reducing xerostomia-related discomfort, they are not tolerated by all patients because of their short-lasting effect and product characteristics such as texture and viscosity, availability and cost[8].

One of the medications in use is pilocarpine; however, despite its positive results, it is contraindicated during lactation and in patients with asthma, chronic obstructive pulmonary disease, coronary heart diseases, hypothyroidism, and glaucoma, among other diseases. The use of this medicament may cause sudoresis, nausea and vomiting, frequent urination, arrhythmias, hypertension, agitation, and bronchospasm[9]. Another example is cevimeline, which can cause gastrointestinal disorders[10].

Transcutaneous electrical nerve stimulation (TENS) has demonstrated positive results as regards increased salivary flow[11]. It can be applied in a greater number of patients, with a better cost/benefit ratio, because it has fewer contraindications. It is a fairly new technique and there is still little research on it when it comes to stimulation of salivary flow, especially in oncology patients.

There is scarce scientific evidence available in the literature. Existing research[12,13] raises the possibility of using this technique as a way to reestablish salivary flow. However, in the published studies, application occurred in patients who had undergone RT through the IMRT or the 3D methods[12,13], which entail a higher chance of success in the technique, because lesser damage is expected in salivary glands. Moreover, the studies differ as to the method of saliva collection, devices and size of electrodes, neither do they report important information, e.g., intensity tolerated or even the method of sialometryused.

In this way, the objective of the present work was to test the hypothesis that a single application of TENS could stimulate an increase in the salivary flow of individuals with hyposalivation resulting from RT for head and neck tumors.

METHODS

This research is an uncontrolled before-and-after clinical trial (Figure 1). The sample was composed by patients who had undergone RT through the 2D method, at Hospital Santa Rita da Irmandade Santa Casa de Misericórdia de Porto Alegre. The sample included 15 patients, 11 of whom were males (73.3%). Average age of the sample was 56.8 ± 6.4 years. All patients had complaints of radiotherapy-induced xerostomia and hyposalivation, which were confirmed by sialometry. To participate in the study, patients should have finished RT at least 90 days before, present skin integrity, have no history of tumor lesion in the salivary glands (submandibular, sublingual, and parotid glands) and neck dissection level I. Conversely, patients were excluded when they had severe dysphagia, had a volume of stimulated salivary flow greater than 1.0 mL/minute, used protective substances or glandular salivary stimulants, used a pacemaker or for any other reason that prevented them from undergoing TENS.

The evaluation included oral inspection with visualization of the aspect of the mucosa and the possible presence of dryness, cracking and/or hyperemia as well as the presence of saliva in the oral cavity.

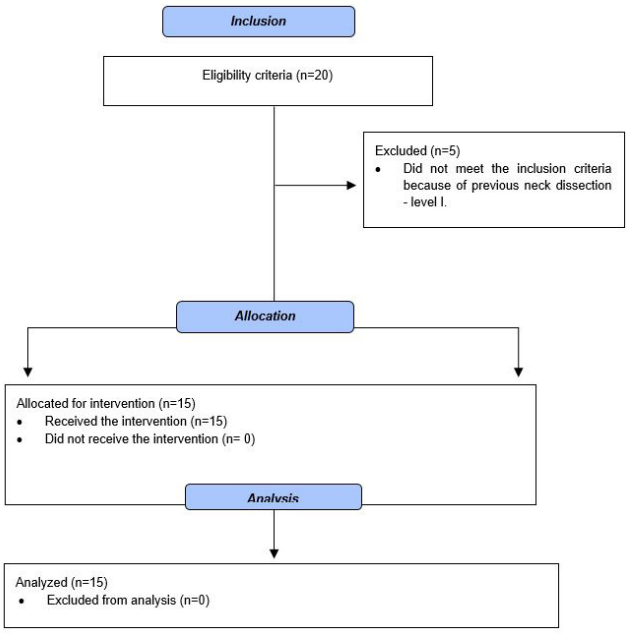

Figure 1. Flowchart according to Consort 2010[14]

Clinical data on the disease and treatments were collected by means of the information provided by patients and by the computerized system of the hospital. Information was also collected on respiratory aspects, smoking and drinking habits and medicaments in use. The patients were asked about the possible interference of reduction of saliva on stomatognathic functions and the use of alternative techniques to reduce the discomfort produced by hyposalivation, e.g., water intake. Data on education and marital status was also collected to characterize the sample.

All patients were initially evaluated by a head and neck surgeon through fiber-optic nasolaryngoscopy with the purpose of excluding the cases of disease recurrence. For this reason, *Xylestesin 2%* was used to anesthetize the patients' selected nostril and reduce the discomfort caused by the introduction of the fiber-optic endoscope. An endoscope manufactured by *Olympus Medical Systems Corp* was introduced in one of the nostrils, and a *Karl Storz (Model DX II)* endoscopy camera and an *Olympus CLV-S20* light source were used to inspect the upper aerodigestive tract (nasal cavity, nasopharynx, oropharynx, hypopharynx and larynx). The exam was complemented by direct oroscopy and palpation of the oral cavity when indicated.

Assessment of salivary flow

Salivary flow was determined by stimulation with the sialometry technique[12] through the Halitus® kit. It was measured before and immediately after the application of TENS through an independent evaluator who was blind to the study groups. The participants were instructed not to ingest food and beverage and not to smoke or perform oral hygiene for a period of 1 h prior to the assessment. The volunteers were instructed to chew a silicone sialogogue for exactly five minutes without swallowing saliva, but rather placing it in a collection tube during the procedure. To precipitate the foam and convert it into saliva, the medicament *Dimeticona* was used (three drops to 4 mL; four drops to 8 mL; five drops above 8 mL of foam), each drop of *Dimeticona* corresponds to 0.02 ml and this value was subtracted from the final result. The amount of saliva and foam was quantified in milliliters (mL) and divided by 5 to determine flow in mL/minute. The following values were determined: < 0.7 mL/min (very low) 0.7-1.0 mL/min (low) > 1.0 mL/min (normal) for stimulated saliva (submandibular, sublingual and parotid)[15-17].

Electro-stimulation

Electro-stimulation was performed with a Neurodyn II-Ibramed® device. Autoclavable silicone electrodes were attached to both sides of patients' face skin, in the region of the major salivary glands: the parotid and submandibular ones (Figure 2). The device was set to produce an electric current for Transcutaneous Electrical Nerve Stimulation (TENS) with 50Hz frequency and 250μs pulse width. Intensity was adjusted manually and continuously until reaching the maximum current tolerated by patients. The continuous electro-stimulation session lasted for 20 minutes.

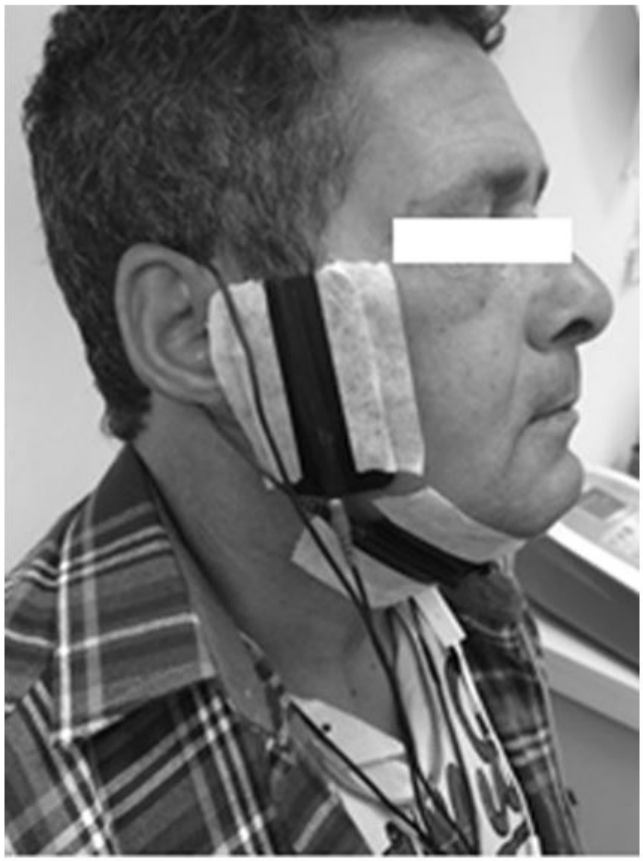

Figure 2. Position of electrodes

The study was approved by the local Research Ethics Committee (CAAE: 51070115.4.3001.5345) and duly registered in *Clinical Trials* (NCT03151889). All patients received and signed an Informed Consent Form (ICF) according to Resolution 466/12 CNS/MS and in accordance with the Declaration of Helsinki.

Statistical analysis

Quantitative data were described in absolute and relative values (percentages) through the mean and standard deviation for parametric distributions and through the median and interquartile interval (25-75%) when they were non-parametric. The comparisons between the evaluations were performed using Student's t test for parametric data and the Wilcoxon-Mann-Whitney test for non-parametric data. Spearman's correlation test was used to assess the degree of dependence of the response to TENS for intensity of the electrical stimulation, to the dose of ionizing radiation used in RT and to time of completion of RT. Evaluation of the response of the salivary glands to TENS was based on the difference between the values found in the final and initial sialometry measurements (Δ = mL/min Final - mL/min Initial). The data were analyzed using the statistical software SPSS v.23. The cut-off point used for determination of statistical significance was 5% (p-value ≤ 0.05).

RESULTS

The most prevalent anatomical region with neoplasia was the oropharynx (80.0% of cases). In addition to radiotherapy, 12 patients (80%) underwent chemotherapy and 8 (53.3%) had surgery. On average, patients had undergone RT for 17.6 ± 24.2 months before participating in the study. The average dose used in these individuals was 64.6 ± 7.2 Gy. The other characteristics of the sample are shown in Table 1.

As expected, after the end of RT, all patients included in this study who had hyposalivation had a change in the quantity of saliva while 12 of them (80%) had a change in viscosity. The main problems in decreased salivary flow were difficulty in swallowing 14 (93.3%), speaking 12 (80%) and chewing 7 (46.7%). Only 6 patients (40%) made use of salivary substitutes and 10 (66.7%) reported sleep problems.

Maximum intensity tolerated during the application of TENS was 34.2 ± 5.8 mA. Tolerance was considered to be satisfactory, because all volunteers fully complied with the protocol without complaints or complications.

The sialometry records showed great variability among patients, which resulted in a non-parametric distribution (Table 2). Even so, the acute effect of TENS promoted a significant increase of salivary flow from 0.05 (0.00-0.40) mL/min to 0.10 (0.04-0.40) mL/min (p = 0.0051). Subsequent analyses showed a moderate positive correlation between response to TENS and maximum intensity of the electric current tolerated during electrical stimulation (r = 0.55; p = 0.032) and a moderate inverse correlation with the dose of ionizing radiation used in the RT treatment (r = -0.51; p = 0.050) (Figure 3). Conversely, the time interval between the end of RT and the TENS session had no significant effect on response of salivary glands to electrical stimulation (r = -0.17; p = 0.522), when evaluated by the difference between the initial and final salivary flows.

Table 1. Clinical and demographic characteristics (n = 15)

Variable	n(%) / mean ± SD
Age (years)	56.8 ± 6.46
Males	11(73.3%)
Location of the neoplasm	
Nasopharynx	1 (6.7%)
Oropharynx	12 (80.0%)
Larynx	2 (13.3%)
Presence of tracheostomy	1(6.7%)
Active smoker	1 (6.7%)
Active alcoholic	2 (13.3%)
Dietary habits	
Alternative route	2 (13.3%)
Oral feeding with food of all consistencies	11 (73.3%)
Chemotherapy	12(80%)
Surgery	8 (53.3%)
RT Dose (Gy)	64.6 ± 7.27
Time of completion of RT (months)	17.66 ± 24.20
Water intake (L/day)	1.6 ± 0.82
Complaint of change in taste	15 (100.0%)
Complaint of change in smell	8 (53.3%)

Caption: SD: standard deviation; RT: radiotherapy

Table 2. Acute effect of TENS on salivary flow (n = 15)

Patient ID	Sialometry (mL/min)		TENS Intensity
	Pre-test	Post-test	(mA)
1	0.0	0.0	23
2	0.3	0.4	40
3	0.6	1.0	35
4	0.1	0.1	35
5	0.0	0.0	33
6	0.4	0.4	32
7	0.0	0.2	27
8	0.0	0.0	33
9	0.0	0.1	40
10	0.4	0.4	34
11	0.4	0.8	37
12	0.6	0.8	45
13	0.0	0.1	40
14	0.0	0.0	26
15	0.0	0.1	34
MD	0.05	0.10	-
(25%;75%)	(0.00; 0.40)	(0.07;0.40)	
(Mean ± SD)	-	-	34.2 ± 5.8

Caption: MD: median; SD: standard deviation

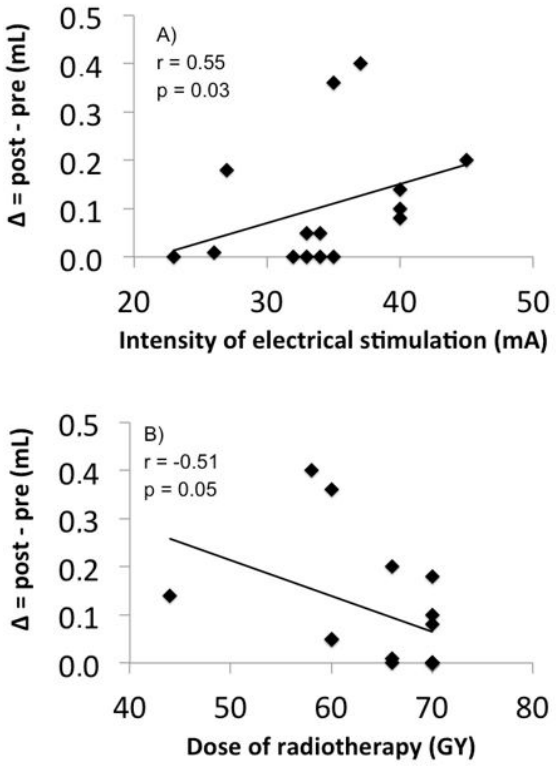

Figure 3. Correlation between the response of the salivary flow (Δ = mL Final - mL Initial), intensity of electric current (mA) and (B) *dose of ionizing radiation used in RT (Gy).* Spearman's correlation

DISCUSSION

The results of this study showed that TENS significantly increased the salivary flow of patients with head and neck cancer and RT-induced hyposalivation. An important point of these findings was a moderate positive correlation between intensity of the applied electrical stimulation and response of the salivary flow. In parallel, the dose of ionizing radiation used in RT also influenced the response of the salivary glands to electrostimulation, but negatively. Apparently, the higher the intensity of the electric current, the greater is the production of saliva in response to TENS, while the higher the dose of ionizing radiation, the lower the salivary flow after application of TENS. This indicates that the greater the dose used in RT, the greater the gland damage, which justifies part of the low functionality of these glands even when stimulated artificially. Finally, time of tissue recovery after the radiotherapy treatment did not help restore the function of the salivary glands in this small sample, thus reinforcing the irreversible characteristic, when not stimulated, of radiation-induced tissue damage.

The patients included in this study underwent external RT (teletherapy) by the conventional 2D method, but the treatment is planned with a basis on an X-ray image, which offers little accuracy for visualization of soft tissues, thereby increasing the exposure of healthy tissues to ionizing radiation. Although this treatment focuses on the region of the tumor, healthy cells of adjacent structures are affected unnecessarily; for example, the salivary glands. When patients undergo three-dimensional intensity-modulated radiotherapy (IMRT), there may be adverse effects such as deglutition and salivation disorders[11,18,19], but to a lesser degree.

The physical-chemical changes of saliva, as well as the reduction or even a complete absence of salivary flow, affect the functions of speech and deglutition by reducing the lubrication of the oral cavity and impairing the proper preparation of the alimentary bolus[20,21]. The patients in this study reported these changes in the initial assessment. These changes were not evaluated separately; only the participants' self-perception about their stomatognathic functions was considered.

The most affected salivary glands are the major ones, which are often involved in the radiation field[22]. There are different theories that propose divergent mechanisms on how radiation affects the salivary glands by decreasing their secretion. Some suggest that this effect is related to damage to the plasma membrane of acinar cells. In a late phase, the effect would be due to the reduction in the amount of functional acinar cells[23].

The main factors that influence the severity of this disorder are the dose of RT, the amount of salivary tissue exposed and individual characteristics[24]. In addition to the reduction of volume, the saliva becomes thicker[25], a characteristic present in the complaints of the patients in this study. However, regardless of the pathophysiological mechanism that leads to reduced salivary flow, the results of this study showed that TENS, within the parameters described previously, was able to improve the functioning of the salivary glands after a single session, although, in some cases, the normal value could not be reestablished (1.0 mL/min). Still, the technique is a potential alternative, since even a small increase in salivary flow can provide individuals with greater comfort and possibly oral positive influence on deglutition, speech and mastication.

The present findings show that the median of the stimulated salivary flow increased by 100% in patients with RT-induced hyposalivation. In the study conducted by Lakshman et al.[12], TENS (500Hz) was used in bilateral parotid glands. The authors found an increase in salivary flow with a variation of 3.7% to 140% in the intervention groups.

Vijayan, et al. (2014)[13] applied TENS (500HZ) in bilateral parotid glands and found an average increase of 0.06 mL/min, which represents an increase by 130%. Their findings are similar to the ones in the present study. Another method of stimulation through acupuncture points identified improvement of hyposalivation, with an increase which ranged from 65% to 83% over 4, 6, 9 and 15 months of follow-up[26]. Together, these findings reinforce the effect of TENS on the excretion function of the salivary glands, which manifest themselves both acutely and late.

Healthy individuals were also benefited by TENS. Longman et al.[27] found an increase in salivary flow by 71% (pre-test = 0.07 ± 0.03 mL/min; post-test = 0.12 ± 0.03 mL/min) after a single application of electrical stimulation. Similarly, Aggarwal et al.[28] found, in apparently healthy individuals, an increase in salivary flow in the order of 13% (0.16 mL/min/ Pre-test = 1.25 mL/min; post-test = 1.41 mL/min), after a single application of TENS (100Hz frequency, 100 to 150uS pulse width, and electrodes allocated in the region over the parotid glands). In another study, which included a heterogeneous sample composed of patients with the most various pathologies (e.g., diabetics; users of antidepressants, antipsychotics and diuretics; and post-menopausal women), 5-minute electrical stimulation with the same parameters used in the present study (50Hz and 250uS) also resulted in benefits (pre-test: 2.343 mL/min; post-test: 3.053)[29].

Another point to consider is the long-term effect of TENS. Some studies[12,26] tried to find out if the increase of saliva would continue over time; however, they are uncontrolled trials and/or have reduced samples. Thus, despite their results, they do not have enough theoretical bases to justify the choice of this method for treatment of hyposalivation after RT. This evidence must be proven in controlled studies with a larger sample size, in view of the high variability found in the salivary flow records of these patients.

The mechanism of action of TENS in the glands is not yet clear, but it is believed that the electric current acts upon the direct stimulation of the secretomotor-auriculotemporal nerve. These nerve bundles are located bilaterally and are afferent paths that carry sensory information (action potentials) to the salivatory nuclei (center of salivation) in the medulla oblongata, which, in turn, send efferent responses of the reflex responsible for salivation[30].

The objective of the present study was to evaluate the mechanisms of action of TENS on salivary flow. Prior to that, it had to be tested whether or not there would be some type of functional response in this population. In this study, relevant facts were found about the variability of response of the glandular tissue and about the main factors that imply an effect on electrical stimulation of salivary flow in this population.

Such contributions have significant clinical relevance for the treatment of the stomatognathic disorders often found in these patients.

This is a preliminary study that evaluated only the acute effect of a specific type of electro-stimulation, with a small number of observations and without comparison with a control group. However, the application of this preliminary study is relevant because there is a shortage of research on the use of this technique of stimulation of salivary glands in patients after treatment for head and neck cancer. It should also be noted that other types of electric current or even other ways to adjust TENS can positively stimulate salivary flow, but the findings if this study open up a prospect for new studies on the treatment of hyposalivation, because the TENS technique is an easy to apply, safe if applied by skilled professionals, non-invasive and widely used.

CONCLUSION

TENS, within the parameters in use, was able to stimulate the salivary glands, thus promoting a significant increase in the salivary flow in patients with RT-induced hyposalivation.

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Author contributions

EDP participated in study design, data collection, analysis and interpretation, and writing of the article; FEM participated in data analysis, discussion and revision of the article; VBM participated in study design, data interpretation and revision of the article; VGZ participated in study design, data interpretation and revision of the article; BG participated in data analysis, discussion and revision of the article; MCBB as an adviser, participated in data analysis, discussion and revision of the article.