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Systematic Review
Revisão Sistemática

Electrical stimulation in the treatment of radiotherapy-induced hyposalivation

Estimulação elétrica no tratamento da hipossalivação induzida pela radioterapia

Émille Dalbem Paim[1,2]
Monalise Costa Batista Berbert[2]
Virgilio Gonzales Zanella[1]
Fabricio Edler Macagnan[2]

Keywords

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ABSTRACT

Purpose: To analyze the effects of electrical stimulation on the salivary flow of head and neck cancer patients with radiotherapy-induced hyposalivation. **Research strategies:** Searches were made in the Medline (via Pubmed), Cochrane Library, Scopus and Lilacs databases. **Selection criteria:** Selection included clinical trials that evaluated salivary flow objectively, published in the last 10 years in either Portuguese, English or Spanish. **Data analysis:** The PEDro scale was used for the methodological evaluation of the studies. **Results:** The search strategy resulted in 21 publications, 17 of which were excluded, hence there were 4 articles left. The included studies had a total of 212 participants, all of whom had an increase in salivary flow, both through the electroacupuncture method and direct application on the salivary glands. The score obtained through the PEDRo scale was low, evidencing questionable methodological quality and risk of bias. **Conclusion:** The included studies demonstrate the clinical potential of TENS to increase the salivary flow of head and neck cancer patients treated with RT.

Descritores

Xerostomia
Neoplasias de Cabeça e Pescoço
Radioterapia
Fonoaudiologia
Oncologia

RESUMO

Objetivo: Analisar os efeitos da eletroestimulação sobre o fluxo salivar de pacientes com hipossalivação induzida por radioterapia em região de cabeça e pescoço. **Estratégia de pesquisa:** Utilizaram-se as bases de dados Medline (via Pubmed), Cochrane Library, Scopus e Lilacs. **Critérios de seleção:** Foram selecionados os ensaios clínicos que avaliaram objetivamente o fluxo salivar, publicados nos últimos 10 anos em português, inglês ou espanhol. **Análise dos dados:** Para avaliação metodológica dos estudos, foi utilizada a escala PEDro. **Resultados:** A estratégia de busca resultou em 21 publicações, sendo que 17 foram excluídas, selecionando-se assim 4 artigos. Os estudos incluídos contaram com um total de 212 participantes, sendo que todos demonstraram aumento do fluxo salivar, tanto por meio do método de eletroacupuntura quanto pela estimulação aplicada diretamente sobre as glândulas salivares. A pontuação obtida por meio da escala PEDro foi baixa, evidenciando qualidade metodológica baixa e com consideráveis riscos de viés. **Conclusão:** os estudos incluídos demonstram o potencial clínico da TENS no aumento do fluxo salivar de pacientes com câncer de cabeça e pescoço tratados com RT.

Correspondence address:
Émille Dalbem Paim
Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA
Rua Sarmento Leite, 245, Centro Histórico, Porto Alegre (RS), Brasil, CEP: 90050-170.
E-mail: fono.emille@yahoo.com.br

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[1] Irmandade Santa Casa de Misericórdia de Porto Alegre - Porto Alegre (RS), Brasil.

[2] Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA - Porto Alegre (RS), Brasil.

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INTRODUCTION

Radiotherapy (RT) is a therapeutic modality frequently used to treat head and neck cancer. It can be a neoadjuvant or an adjuvant to surgery, and can be associated with chemotherapy[1]. Radiotherapy has evolved: it can be used together with imaging tests and improved systems for planning and calculation of dose distribution. As a result, complications caused by the treatment are reduced[1,2].

However, irradiation to adjacent healthy tissue causes tissue damage that may lead to numerous acute and chronic dysfunctions, including reduction of salivary flow. Common alterations in salivary gland function occur in different degrees of dysfunction that can result in persistent sequelae; their occurrence is related to the regime and dose of radiation in use[3-7].

Hyposalivation is a dysfunction that may occur when the salivary glands are included in the field of irradiation. RT causes the saliva to lose its lubricating property, thus adhering to the teeth and the mucosa[7]. Dry mouth syndrome, also known as xerostomia, is often present, and it usually occurs after cumulative doses of irradiation higher than 1000 cGy[8,9]. Salivary acini are highly radiosensitive; hence radiotherapy can culminate in apoptosis, necrosis, impaired cell receptor signaling, inflammation, edema and vascular changes[7-10].

Xerostomia is reported when the salivary glands are located in the field of irradiation, which occurs from 94 to 100% of the times, but there is a marked decrease when three-dimensional intensity-modulated radiotherapy is used[7,11]. This dysfunction reduces people's quality of life, as it negatively influences the swallowing function, mainly by impairing the preparation of the alimentary bolus. Similarly, it interferes in speech and chewing, as these activities demand saliva for lubrication, execution and protection and may cause serious oral changes in the long-term[12-15]. A study identified a reduction of about 50% in the amount of saliva at 10Gy, and there were prior complaints of xerostomia and decreased taste, in addition to increased viscosity of the saliva, which made it more difficult to swallow[16].

Therapeutic alternatives to increase salivary flow include medications, mechanical stimulation, gustatory stimulation, and electrical stimulation[17,18]. The mechanism by which the electric current acts on gland function is still unclear, but it is believed that the auriculotemporal nerve is involved in the process by means of a reflex mechanism between the afferent pathways, which drive the electrical impulses to the salivary nuclei (salivation center) in the medulla, and the efferent pathways for control of salivary secretion[19,20]. The applicability of this therapeutic approach has been studied since 1986, and electrical stimulation produced positive results in salivary flow[21], even though devices back then were not as technologically advanced as the ones currently available.

It is likely that lack of knowledge about the mechanism of action of electrical stimulation on salivary gland function and the wide range of different forms of generating an electric pulse are the two main factors that justify the lack of a consensus on the use of electrotherapy as a treatment for hyposalivation.

OBJECTIVE

The objective of this review was to analyze the effects of electrical stimulation on salivary flow of patients with radiotherapy-induced hyposalivation in the head and neck region.

METHODS

Search strategy

This is a review of the literature, developed according to the guidelines of the Prisma protocol[22] and designed to evaluate evidence on the use of electrical stimulation as a treatment of RT-induced hyposalivation in the head and neck region.

The search was performed in the Medline databases (via Pubmed), Cochrane Library (Central Register of Controlled Trials), Scielo and Lilacs until January 20, 2018. The search used the MeSH Terms shown in Chart 1.

Selection criteria

Selection of the studies started by the analysis of titles; studies were excluded when their titles were unrelated to the keywords defined by the search strategy. Duplicate articles as well as studies published in languages other than Portuguese, Spanish and English were also excluded.

Based on the abstracts, selection included only clinical trials and intervention studies that evaluated the effect of electrical stimulation on salivary flow of patients submitted to radiotherapy in the head and neck region, published in the last 10 years. Studies that did not present sufficient information in the abstract were also considered for full text analysis.

Articles read in full which met the eligibility criteria were included in the review. The following information was extracted by reading the studies in full: sample characteristics, study design, evaluation methods, intervention protocol and effects on salivary flow (Tables 1 and 2). Selection of articles was defined by two independent evaluators and the differences between the reviewers were resolved by consensus.

Data analysis

The PEDRo scale was used to evaluate the methodological quality of the included studies[23,24]. To score on the scale criteria, information should be clear and objective, otherwise the score was considered to be null. The evaluation was performed by three independent researchers and the results are shown in Chart 2.

Chart 1. Search strategy

1 - Patient	Radiotherapies OR Radiation Therapy OR Radiation Therapies OR, Therapies OR Radiation OR Therapy OR Radiation OR Radiotherapy OR Targeted OR Radiotherapies OR Targeted OR Targeted Radiotherapies, Radiation Therapy OR Targeted OR Targeted Radiotherapy OR Targeted Radiation Therapy OR Radiation Therapies OR Targeted OR Targeted Radiation Therapies OR Therapies OR Targeted Radiation OR Therapy OR Targeted Radiation
2 - Intervention	"Transcutaneous Electric Nerve Stimulation" [MESH] OR "Transcutaneous Electric Nerve Stimulation" OR "Electrical Stimulation, Transcutaneous" OR "Stimulation, Transcutaneous Electrical" OR "Transcutaneous Electrical Stimulation" OR "Percutaneous Electric Nerve Stimulation" OR "Percutaneous Electrical Nerve Stimulation" OR "Transdermal Electrostimulation" OR "Electrostimulation, Transdermal" OR "Transcutaneous Electrical Nerve Stimulation" OR "Transcutaneous Nerve Stimulation" OR "Nerve Stimulation, Transcutaneous" OR "Stimulation, Transcutaneous Nerve" OR "Electric Stimulation, Transcutaneous" OR "Stimulation, Transcutaneous Electric" OR "Transcutaneous Electric Stimulation" OR "TENS" OR "Analgesic Cutaneous Electrostimulation" OR "Cutaneous Electrostimulation, Analgesic" OR "Electrostimulation, Analgesic Cutaneous" OR "Electroanalgesia" OR "Electric Stimulation"[Mesh] OR "electric stimulation" OR "Electrical Stimulation" OR "Electrical Stimulations" OR "Stimulation, Electrical" OR "Stimulations, Electrical" OR "Stimulation, Electric" OR "Electric Stimulations" OR "Stimulations, Electric" OR "Electric Stimulation Therapy"[Mesh] OR "Electric Stimulation Therapy" OR "Stimulation Therapy, Electric" OR "Therapeutic Electrical Stimulation" OR "Electrical Stimulation, Therapeutic" OR "Stimulation, Therapeutic Electrical" OR "Therapy, Electric Stimulation" OR "Electrotherapy" OR "Therapeutic Electric Stimulation" OR "Electric Stimulation, Therapeutic" OR "Stimulation, Therapeutic Electric" OR "Electrical Stimulation Therapy" OR "Stimulation Therapy, Electrical" OR "Therapy, Electrical Stimulation" OR "Electroacupuncture" [Mesh] OR "Electro-acupuncture"
3 - Comparison	Different treatments were not compared
4 - Outcome	Xerostomias OR Hyposalivation OR Hyposalivations OR Asialia OR Asialias OR Mouth Dryness OR Dryness OR Mouth
Search	1 and 2 and 4

Table 1. Characterization of the studies included in the review

Author/Year	Study design	N patients	Time of RT termination	Rate used in RT	Irradiation method used in RT	Parameters of the electric current used in therapeutic intervention	N of interventions performed in the treatment	Position of the electrodes during the treatment with electrical stimulation
Wong et al.[25]	RCT	96 62/h 11/m	≥3 months	?	?	TENS - acupuncture, 250mS, 4Hz, 20 minutes	2x/week 12 weeks 24 sessions	Sp6, St36, LI4 (active) and CV24 (inactive)
Wong et al.[26]	RCT	46	?	>50Gy	Radical RT	TENS – acupuncture, 250mS, 4Hz, 20 minutes	2x/week 12 weeks 24 sessions	Group A Sp6, St36, LI4 (active) and CV24 (inactive) Group B Sp6, St36, P6 (active) and CV24 (inactive) Group C Sp6, St5 and 6, P6 (active) and CV24 (inactive)
Lakshman et al.[27]	IS	40	?	?	?	TENS, 50Hz	?	Parotid glands, bilaterally
Vijayan et al.[28]	IS	30 22/h 8/m	3 months	60/70Gy	IMRT	TENS, 50hz 250ms	1x	Parotid glands, bilaterally

Caption: RCT = randomized controlled trial; IS = uncontrolled intervention study; RT = radiation therapy; IMRT = intensity-modulated radiation therapy; TENS = transcutaneous electrical nerve stimulation; Sp6, St36, CV24, LI4, St5 and P6 = location of the different acupuncture points (see the articles cited in the review); ? = data not shown; N=number

Table 2. Effect of different types of electro-stimulation on salivary flow

Author/Year	Groups	Moment of assessment	Salivary flow (mL/min)	Δ salivary flow (mL/min)	Δ%	Outcome
Wong et al.[25]	IG (n=73)	Onset	NS (I) = 1.2 S (I) = 2.4	-	-	There was no significant effect in comparison to the first session, but salivary flow values were normal in all evaluations
		Week 16	NS (F) = 1.3 S (F) = 2.7	0.10 0.30	8% 11%	
		Week 24	NS (F) = 1.3 S (F) = 2.9	0.10 0.20	8% 17%	
		Week 36	NS (F) = 1.3 S (F) = 3.0	0.10 0.60	8% 20%	
		Week 60	NS (F) = 1.4 S (F) = 2.9	0.20 0.20	15% 7%	
Wong et al.[26]	IG A (n=13)	Onset	NS (I) = 0.26 S (I) = 1.07	-	-	
	IG B (n=10)	Week 12 after the end of RT	S (I) = 0.26 S (F) = 1.33 NS (I) = 0.10 NS (F) = 0.36	1.07* 0.26*	80% 72%	TENS increased salivary flow at three months after the end of RT
	IG C (n=14)	Week 24 after the end of RT	NS (F) = 0.37 S (F) = 1.61	0.11 0.54	30% 33%	TENS increased salivary flow at six months after the end of RT when compared to the initial assessment
Lakshman et al.[27]	IG (n=10)	At 4 weeks after the end of RT	S (I) = 0.55 S (F) = 0.57	0.02	4%	TENS did not increase salivary flow significantly
		Prior to RT	S (I) = 0.84 S (F) = 1.62	0.78*	95%	Salivary flow increased significantly after daily use of TENS during RT
	IG (n=10)	Week 3 of RT	S (I) = 0.56 S (F) = 1.38	0.82*	146%	
		Week 6 of RT	S (I) = 0.70 S (F) = 1.27	0.57*	71%	
	CG (n=10)	1 month after the start of RT	S (I) = 0.82 S (F) = 1.64	0.82*	100%	
		-	S (I) = 0.61 S (F) = 1.65	1.04*	170%	In the control group (healthy individuals), TENS increased salivary flow significantly
Vijayan et al.[28]	IG (n=30)	After RT	NS (I) = 0.05 NS (F) = 0.12	0.06*	130%	TENS increased salivary flow after one single application

*statistically significant (p <0.05)
Caption: IG = intervention group; CG = control group; S = evaluation of stimulated salivary flow (citric acid); NS = evaluation of non-stimulated salivary flow; I = initial; F = final; TENS = transcutaneous electrical nerve stimulation; RT = radiation therapy

Chart 2. Evaluation of the methodological quality of articles according to PEDro scale[22]

PEDRo CLASSIFICATION/ ARTICLES		Wong et al.[25]	Wong et al.[26]	Lakshman et al.[27]	Vijayan et al.[28]
External Validity (Max = 1)	1 Inclusion criteria	Y	N	Y	Y
Internal Validity (Max = 8)	2 Random allocation	Y	N	N	N
	3 Concealed allocation	N	N	N	N
	4 Similar group at the beginning of the study	Y	N	Y	Y
	5 Blinding of participants	N	N	N	N
	6 Blinding of therapists	N	N	N	N
	7 Blinding of assessors	N	N	N	N
	8 Analysis of 85% of the sample	Y	Y	Y	Y
	9 Analysis by "intention to treat"	N	N	N	N
Interpretation of outcomes (Max = 2)	10 Comparison between groups	Y	Y	N	N
	11 Measures of central tendency and dispersion	N	Y	Y	Y
Total points (Max = 11)	-	5	3	4	4

Caption: Y = yes; N = no; MAX = maximum

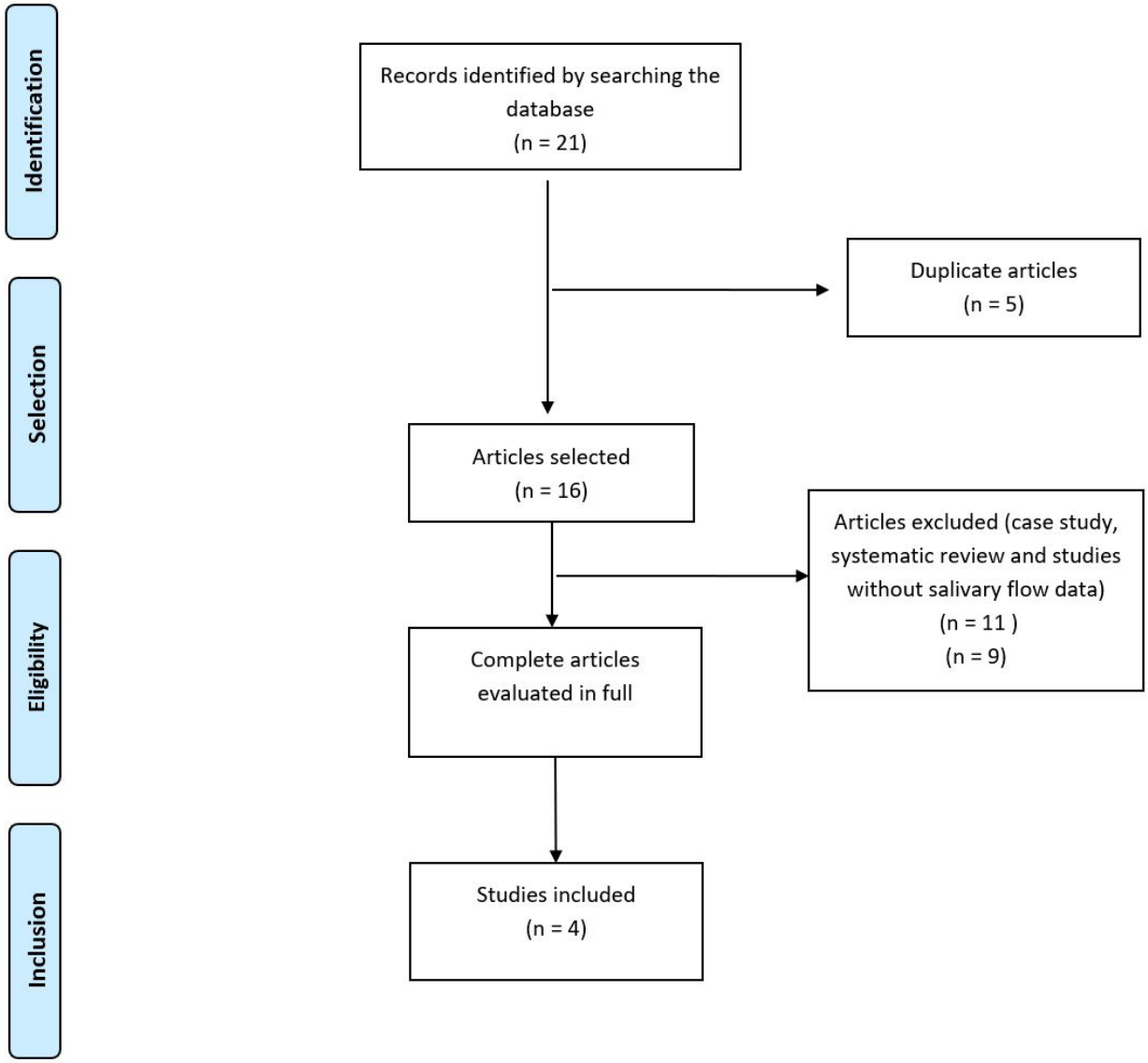

Figure 1. Diagram according to Prisma protocol guidelines. Flow Diagram (Prisma 2009)[21]

RESULTS

The recommended search strategy resulted in 21 publications, 5 of which were excluded because they were duplicated and 11 because they were systematic reviews or case studies, or they did not measure salivary flow. Thus, 4 articles were selected, analyzed and included in this review (Figure 1).

The evaluation of the methodological quality of the included studies shows (Chart 2) that, in general, the studies reached low PEDRo scores. Aspects relative to internal validity achieved a low score, especially because of the lack of blindness of both the assessors and the subjects. However, the results reported in all studies were found through an analysis of 85% or more of the participants included in the selection criteria.

As described in Table 1, all studies included patients who received RT for the treatment of head and neck tumors. There was a total of 212 participants aged between 58 and 60 years. Dose of RT, time elapsed after the end of the treatment and method were not reported in 2 studies[25,26]. In studies that included such information, RT was performed by the IMRT and the 2D method, and dose ranged from 50 to 70Gy. Division of groups, number of participants, time of intervention and study design were considerably heterogeneous.

Interestingly, both the electroacupuncture method[25,26] and locally applied electrical stimulation of the salivary glands[27,28] were beneficial for salivary flow, but not all the results were significant (Table 2). In the studies that used conventional TENS, the parameters were similar (50Hz frequency and 250μs pulse width). In the acupuncture mode, the two studies used the same acupuncture points[27,28] and electrical stimulation parameters (4 Hz frequency and 250 μs pulse width).

The present study addresses the applicability of TENS to increase salivary flow of individuals with RT-induced hyposalivation. This review shows that the benefit of TENS on salivary gland function is still questionable not only because there is a small number of studies, but also because of the relatively

low methodological quality found in the available RCTs. Part of this methodological fragility is due to the low number of patients and the absence of placebo therapy. In addition, experimental designs are vulnerable because they lack detailed information about how researchers dealt with selection bias, performance bias, detection bias, friction bias and reporting bias. Because of these aspects and the lack of a control group in 50% of the selected studies, a decision was made to use the PEDRo scale instead of the Cochrane risk-of-bias tool for randomized trials[29]. Nevertheless, even after a careful selection of studies and use of a less sensitive scale, the mean score resulting from the evaluation was low (4,5), hence further research is needed to support the clinical decision to use this therapeutic resource.

Many of the studies were excluded because they lacked an objective evaluation of salivary flow. Evaluating xerostomia only through subjective tools, usually through a visual analog scale (VAS) and quality of life questionnaires, makes it more difficult to determine the effectiveness and standardization of this technique.

Also, data available in the selected studies are not clear about the characteristics of the type of RT in use (irradiation mode, dose, number of sessions and time of treatment termination), and there is virtually no description of the associated drug treatment. Overall, the lack of these clinical descriptors limits an in-depth understanding of possible interferences that may reduce salivary flow and of TENS response analysis.

In general, electrical stimulation of the salivary glands can be performed locally (electrodes positioned on the gland) or at a distance. When it comes to distance stimulus (acupuncture), it is expected that the effect of sympathetic inhibition and parasympathetic stimulation, as described by the acupuncture method, will activate the autonomic nervous system for an increase in saliva production. This result was found in the included studies[25,26]. However, when compared to local stimulation[27,28], the results were considerably lower. This implies that function recovery may be increased through direct stimulation of the glands.

The saliva production mechanism is quite complex and depends on the action of the autonomic nervous system, mainly the parasympathetic branch. It is known that the efferent fibers of the facial nerve arise from the superior salivatory nucleus, which innervates the submandibular and sublingual glands through the chorda tympani. Another neural pathway originates in the inferior salivatory nucleus, which gives rise to the glossopharyngeal motor fibers that provide innervation to the parotid gland[30-35]. These efferent nerve pathways participate in the production and secretion of saliva; however, RT can interfere in this signaling process by altering tissues and structures responsible for gland function. In addition, RT can also cause dysfunctions of both the afferent pathways and receptors that carry important sensory information (taste, touch, texture, smell and vision) to the central nervous system nuclei responsible for controlling salivary flow[35-37]. Because it is a control pathway involving different signaling mechanisms, the choice of salivary flow assessment method is fundamental.

Sialometry through citric acid stimulation was the predominant method in the included studies. Such choice is due to the fact that acidic/citric substances are effective salivation stimulants, especially of the parotid gland. Notably, radiation-induced atrophy of the taste buds occurs after RT and impairs sensory input, leading to gustatory reduction. Perhaps choosing the mechanically stimulated sialometry method, through chewing, is preferable because it excites mechanoreceptors and causes myoepithelial cells (located between the basement membrane and the acinar cells) to expel the secreted saliva by contraction and massively empty the granules[37].

The initial degree of hyposalivation may interfere with the response. However, one study[25] included patients with normal salivary flow (1.2 mL/min in unstimulated sialometry and 2.4 mL/min in stimulated sialometry). This may explain the low effect of TENS on the observed salivary flow[25] in comparison to other studies[26-28].

With regard to TENS parameters, it was found that the stimulation performed directly on the salivary glands was performed with 50 Hz and 250 μS pulse width[27,28]. However, even though the salivary flow was much greater (80%) than the results obtained in the acupuncture mode, it cannot be assumed that these adjustments are effectively considered as the definitive choice for the adjustment of electrical stimulation, because there are no studies comparing other parameters of the electric current. In addition, electrical current intensity was not sufficiently described (absolute values) in the included studies, although intensity adjustment was maintained within the tolerance limit throughout the treatment in the studies[25-28].

Moreover, no intercurrence was reported as a reason for not using the proposed electrical stimulation treatment. However, the low number of patients included (212) in local (on the face) electrical stimulation protocols limits the final analysis of safety and viability - without, however, recommending against the use of this resource for the treatment of RT-induced hyposalivation in patients with head and neck cancer.

Another issue that remains inconclusive is the optimal timing to start the electrical stimulation treatment. Apparently, the results found in the study of Lakshman et al.[27] suggest that the early use of TENS (for or up to 1 month after the end of RT) may yield better results. None of the studies has been sufficiently designed to test the optimal timing to start electrical stimulation; therefore, the clinical condition of the patient remains the mandatory requirement for indication of TENS and special attention should be given to skin conditions in protocols for local stimulation of salivary glands.

The studies were heterogeneous, which hindered a meta-analysis and limited the use of other evaluation instruments that could possibly influence the strength of evidence and an analysis of risk of bias across the studies.

CONCLUSION

The included studies showed the clinical potential of TENS for increasing salivary flow of patients with head and neck cancer treated with RT.

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Author contributions

EDP conception and design of the study, data collection, analysis and interpretation of data, drafting the article; FEM analysis and interpretation of data, revising the article; VGZ conception and design of the study, interpretation of data, revising the article; MCBB conception and design of the study, analysis and interpretation of data, drafting the article.