JAMIL SALEH

EFEITO DA TERAPIA LASER DE BAIXA POTÊNCIA NA HIPOSSALIVAÇÃO E XEROSTOMIA DECORRENTES DA RADIOTERAPIA

Dissertação apresentada à Faculdade de Odontologia da Pontifícia Universidade Católica do Rio Grande do Sul como parte dos requisitos para obtenção do título de Mestre em Odontologia, área de concentração em Estomatologia Clínica.

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“A tarefa não é tanto ver aquilo que ninguém viu, mas pensar o que ninguém ainda pensou sobre aquilo que todo mundo vê.”

Arthur Schopenhauer

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RESUMO

RESUMO

A xerostomia e a hipossalivação são importantes sequelas da radioterapia de cabeça e pescoço e podem ter impacto negativo na qualidade de vida dos pacientes. O presente estudo teve como objetivo realizar uma revisão de literatura destas sequelas e avaliar o efeito da terapia laser de baixa potência (TLBP) na hipossalivação, xerostomia e qualidade de vida relacionada à saúde bucal de pacientes submetidos à radioterapia em cabeça e pescoço. Foram selecionados 23 pacientes com histórico de neoplasia maligna em região de cabeça e pescoço, tratados por meio de teleterapia fracionada, cujo portal tenha envolvido ao menos 50% das glândulas salivares maiores. Todos deveriam ter finalizado a radioterapia há pelo menos seis meses e apresentar hipossalivação e xerostomia. A amostra foi aleatoriamente distribuída em grupos laser (n=12) e controle (n=11). Foi empregado laser de AsGaAl no comprimento de onda de 830 nm (infravermelho), potência de 100 mW e energia de 2 J por ponto. Os pacientes foram submetidos a doze sessões de TLBP, aplicada pontualmente em ambas as glândulas parótidas, submandibulares e sublinguais. No grupo-controle foi adaptado ao aparelho de laser um dispositivo que impedia a emissão de radiação. O fluxo salivar em repouso e sob estímulo foi avaliado em *baseline*, após a 6ª e a 12ª sessão de TLBP. A xerostomia foi avaliada por meio de Escala Visual Analógica (EVA) e a qualidade de vida relacionada à saúde bucal, por meio do instrumento *Oral Health Impact Profile* (OHIP-14). Os resultados demonstraram não haver diferença significativa entre os grupos laser e controle quanto à velocidade do fluxo salivar, xerostomia ou qualidade de vida. Por outro lado, em ambos os grupos ao final do tratamento, houve redução significativa da xerostomia e melhora da qualidade de vida

relacionada à saúde oral. Com base nos resultados, pode-se concluir que a TLBP, nos parâmetros utilizados, não foi capaz de promover elevação clinicamente detectável do fluxo salivar ou redução da xerostomia. Os resultados podem estar associados aos efeitos tardios da radioterapia na estrutura glandular tais como fibrose e atrofia acinar. A melhora dos índices subjetivos xerostomia e qualidade de vida em ambos os grupos ressalta a importância da orientação e acompanhamento dos pacientes irradiados.

Palavras-chave: Saliva. Xerostomia. Radioterapia. Terapia a laser. Qualidade de vida.

ABSTRACT

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Xerostomia and hyposalivation are important sequelae of head and neck radiotherapy and may have a negative impact on quality of life. The present study aimed to evaluate the effects of low level laser therapy (LLLT) on hyposalivation, xerostomia and quality of life related to oral health (QLROH) in irradiated patients. Were selected 23 patients with a history of head and neck malignancy, treated with fractioned teletherapy, whose therapeutic site had involved at least 50% of the major salivary glands. Patients should have completed radiotherapy for at least six months and present hyposalivation and xerostomia. The sample was randomly distributed in laser group (n=12) and control (n=11). A GaAlAs laser, at 830 nm (infrared) wavelength, 100 mW power, 2 J energy per point was used. Patients underwent twelve sessions of LLLT, applied in parotid, submandibular and sublingual glands. In the control group, the laser tool received a plastic tip that blocked radiation emission. Stimulated and unstimulated salivary flow rate was assessed at baseline, after the 6th and 12th session. Xerostomia was assessed by Visual Analogue Scale (VAS) and QLROH, through the Oral Health Impact Profile (OHIP - 14). The results showed no significant difference between the laser and control groups regarding the salivary flow rate, xerostomia or quality of life. However, at the end of the treatment, the xerostomia and the QLROH showed significant improvement in both groups compared to assessments carried out in baseline. Based on the results, we conclude that, in the parameters used, LLLT was not able to increase salivary flow rate or decrease xerostomia. The results may be associated to the late effects of radiotherapy on glandular structure such as fibrosis and acinar atrophy.The

improvement in xerostomia and quality of life highlights the importance of advice given to the irradiated patients and their follow-up.

Keywords: Saliva. Xerostomia. Radiotherapy. Low level laser therapy. Quality of life.

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EFFECT OF LOW-LEVEL LASER THERAPY ON RADIOTHERAPY-INDUCED HYPOSALIVATION AND XEROSTOMIA: A PILOT STUDY

LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

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ANTT	Anethole Trithione
AsGa	Arseneto de Gálio
AsGaAl	Aluminum-arsenide-gallium
ATP	Adenosina Trifosfato
CMC	Carboxymethylcellulose
CT	Computed Tomography
EVA	Escala Visual Analógica
FDG-PET-CT	Fluorodeoxyglucose-labeled Positron Emission Tomography-computed Tomography
Gy	Gray
hAQP1	Human Aquaporine-1
HIV	Human Immunodeficiency Virus
IMRT	Intensity Modulated Radiotherapy
InGaAlP	Aluminum-gallium-indium-phosphide
KGF	Keratinocyte Growth Factor
LLLT	Low Level Laser Therapy
MnSOD-PL	Manganese Superoxide Dismutase-plasmid/liposomes
MR	Magnetic Resonance
OHIP-14	Oral Health Impact Profile
QoL H&N35	Quality of Life Head and Neck 35
QLROH	Quality of Life Related to Oral Health
TLBP	Terapia Laser de Baixa Potência
TLK1B	Tousled-like kinase 1B

SMA Smooth Muscle Actin

SFR Salivary Flow Rate

VFS Velocidade de Fluxo Salivar

VAS Visual Analogic Scale

SUMÁRIO

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1 INTRODUÇÃO

1 INTRODUÇÃO

O tratamento das neoplasias malignas da região de cabeça e pescoço é multimodal e pode ser realizado por meio de ressecção cirúrgica, radioterapia e/ou quimioterapia. A radioterapia consiste na utilização de doses elevadas de radiação ionizante, que interagem com os tecidos tumorais, atuando sobre o DNA nuclear por meio da produção de radicais livres, o que causa morte ou incapacidade de replicação celular. Sua ação sobre os tecidos não é seletiva, atuando também em células saudáveis, o que a torna tóxica para o organismo (SEGRETO; SEGRETO, 2000). Em neoplasias de cabeça e pescoço, geralmente, a dosimetria de radiação varia de 50 a 70 Gy, fracionada em doses de 2 Gy ao dia (SEIKALY et al., 2004). Atualmente tem sido empregada a técnica de radioterapia de intensidade modulada, de forma que a dose de radiação seja mais intensa na área do tumor, preservando as estruturas adjacentes (BHIDE et al., 2012).

Apesar dos benefícios em neoplasias malignas de cabeça e pescoço, a radioterapia, geralmente, apresenta efeitos adversos tais como alteração da microflora bucal, processos degenerativos e inflamatórios da mucosa, xerostomia, risco aumentado ao desenvolvimento de cáries e de outras doenças infecciosas, osteorradionecrose, trismo, dentre outros (JHAM; FREIRE, 2006; SENNHENN-KIRCHNER et al., 2009; CHREANOVIC et al., 2010; WEBER et al., 2010). Os efeitos adversos imediatos ocorrem durante ou logo após a conclusão da radioterapia e regridem com o tempo. Em contraste, os efeitos tardios são, geralmente, considerados irreversíveis e progressivos (JELLEMA et al., 2007; CHOPRA et al., 2011).

As glândulas salivares maiores são frequentemente envolvidas nos portais terapêuticos de radiação por estarem em proximidade com os sítios de tumores primários e cadeias linfáticas da região de cabeça e pescoço. Como consequência, passam por um processo de degeneração, resultando em hipossalivação e xerostomia (EISBRUCH et al., 2001). A gravidade dessas alterações é determinada por fatores como dose de radiação, quantidade de tecido salivar exposto e resposta individual do paciente (DIRIX et al., 2008; LIN et al., 2008). Clinicamente observa-se redução do volume de saliva, que se apresenta espessa, dispersa e localizada na região posterior do assoalho da boca e vestíbulo inferior, além disso, a mucosa torna-se ressecada e atrófica e o dorso da língua despapilado. Os pacientes podem apresentar disgeusia, disfagia e disartria, ulcerações na mucosa bucal (PORTER; SCULLY; HEGARTY, 2004), risco elevado do surgimento de doenças infecciosas tais como cáries, gengivite, periodontite e candidose (PORTER; FEDELE; HABBAB, 2010).

Em tratamentos radioterápicos convencionais, a xerostomia inicia-se a partir da primeira semana. Os danos passam a ser irreversíveis após doses cumulativas de 26 a 39 Gy, muitas vezes com volumes salivares inferiores a 10% do apresentado previamente à radioterapia (PORTER; FEDELE; HABBAB, 2010; VISSINK et al., 2010). As alterações glandulares iniciam-se pelo dano à membrana plasmática, com perda da resposta aos controles autonômicos, há edema, degeneração e necrose das células acinares. Os efeitos tardios são consequência da fibrose e atrofia dos lóbulos (PORTER, 2010). A saliva resultante sofre alterações qualitativas em suas propriedades orgânicas e inorgânicas, com diminuição da atividade das amilases, da capacidade tampão e do pH, com consequente acidificação. Há elevação dos níveis de cálcio, potássio, sódio e redução na

concentração de fosfato (JHAM; FREIRE, 2006). As alterações do fluxo e viscosidade salivares podem persistir por anos e a recuperação dependerá das características da cada paciente (LOPES; MAS; ZÂNGARO, 2006).

Conceitualmente, a xerostomia é a sensação subjetiva de boca seca, enquanto a hipossalivação consiste na redução objetiva do fluxo salivar. Atkinson, Grisius e Massey (2005) classificam os tratamentos da hipossalivação e xerostomia em: 1) preventivos; (2) sintomáticos; (3) estimulantes tópicos e sistêmicos; (4) agentes modificadores de doença e (5) regeneradores. Pode-se destacar o uso de gomas de mascar, de sialagogos sistêmicos, estimulação elétrica, acupuntura, substitutos da saliva, toxina botulínica, transferência de glândula salivar entre outros tratamentos citados na literatura (SEIKALY et al., 2004; JHAM et al., 2007; JELLEMA et al., 2007; MÜNTER, et al., 2007; TEYMOORTASH et al., 2009; JENSEN et al., 2010; RIEGER, 2012).

A terapia laser de baixa potência (TLBP) ou fototerapia laser é um método simples, podendo ser utilizado como adjuvante a tratamentos convencionais ou de forma isolada e eletiva em algumas doenças (BRUGNERA-JUNIOR; PINHEIRO, 1998; LOPES; MAS; ZÂNGARO, 2006; SIMÕES et al., 2008; LONCAR et al., 2011; JENKINS; CARROL, 2011). A TLBP possui baixa energia e não apresenta potencial fototérmico, sendo utilizada por seus efeitos anti-inflamatórios, analgésicos e biomoduladores (LOPES; MAS; ZÂNGARO, 2006; SIMÕES et al., 2008; ANKRI; LUBART; TAITELBAUM, 2010). O efeito resultante da TLBP baseia-se na capacidade de modulação de diversos processos metabólicos, bioquímicos e fotofísicos, que transformam a luz laser em energia útil para a célula. Esta energia provoca reações nas mitocôndrias, com incremento na produção de ATP (Adenosina

Trifosfato), aumento no consumo de glicose pelas células, elevação dos níveis intracelulares de cálcio e do número de mitoses (LOPES; MAS; ZÂNGARO, 2006).

O efeito da TLBP para o tratamento da xerostomia tem sido investigado em pesquisas pré-clínicas e clínicas (LOPES; MAS; ZÂNGARO, 2006; SIMÕES et al., 2008; LONCAR et al., 2011). Simões et al. (2008) demonstraram elevação no fluxo e na concentração total de proteínas salivares de ratos *Wistar* quando submetidos a TLBP nas glândulas salivares maiores. Neste estudo foi empregado laser de diodo, no comprimento de onda de 808 nm, com dosimetrias de 4 e 8 J/cm^2. Simões et al. (2010), em um estudo clínico realizado com pacientes irradiados em cabeça e pescoço, empregaram a TLBP para prevenção e tratamento da mucosite oral. Os pacientes submetidos a três aplicações semanais apresentaram redução da xerostomia e elevação do fluxo salivar estimulado. Os autores sugerem que a laserterapia pode ser empregada como adjuvante no tratamento de alterações das glândulas salivares decorrentes da radioterapia. Ao analisarem o efeito da TLBP em pacientes com mucosite, Cowen et al. (1997) também relataram tais achados, os pacientes apresentaram aumento da produção de saliva e da habilidade de deglutição. Loncar et al. (2011) utilizaram o laser de GaAs (Arseneto de Gálio) (904nm), com densidade de energia de 29,5 J/cm², em 34 pacientes com xerostomia durante 10 dias consecutivos. Os autores verificaram que a laserterapia promoveu aumento do fluxo salivar. Ao avaliarem o efeito da TLBP sobre a velocidade do fluxo salivar em pacientes irradiados, Lopes, Mas e Zângaro (2006) observaram que a velocidade do fluxo salivar manteve-se significativamente superiores nos pacientes que receberam a TLBP em comparação aos controles.

A xerostomia e hipossalivação são importantes sequelas da radioterapia e podem ter impacto negativo na qualidade de vida dos pacientes. Há estudos

demonstrando que a TLBP pode ter efeito benéfico no tratamento dessas alterações. O presente estudo teve como objetivo avaliar clinicamente o efeito da TLBP na hipossalivação e xerostomia decorrentes da radioterapia em região de cabeça e pescoço. Além disso, foi avaliada a influência desta modalidade terapêutica na qualidade de vida relacionada à saúde bucal dos pacientes.

2 PROPOSIÇÃO

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2.1 Objetivo Geral

Realizar uma revisão da literatura sobre a hipossalivação e xerostomia e avaliar clinicamente o efeito da terapia laser de baixa potência (TLBP) no tratamento destas sequelas em decorrência da radioterapia em região de cabeça e pescoço.

2.2 Objetivos Específicos

Avaliar em pacientes submetidos à radioterapia em região de cabeça e pescoço:

- O efeito da TLBP na hipossalivação, pela avaliação da velocidade do fluxo salivar em repouso e sob estimulação.
- O efeito da TLBP na xerostomia, por meio de Escala Visual Analógica (EVA).
- Se a TLBP, utilizada para o tratamento da hipossalivação e xerostomia, exerce influência na qualidade de vida relacionada à saúde bucal.

3 ARTIGO DE REVISÃO DA LITERATURA

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SALIVARY HYPOFUNCTION: AN UPDATE ON ETIOLOGY, DIAGNOSIS AND THERAPEUTICS

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SALIVARY HYPOFUNCTION: AN UPDATE ON ETIOLOGY, DIAGNOSIS AND THERAPEUTICS

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ABSTRACT

Saliva is of paramount importance for the maintenance of oral and general homeostasis. Salivary hypofunction predispose patients to disorders such as dysgeusia, pain and burning mouth, caries and other oral infectious diseases, dysphagia and dysphonia. The aim of this study was to provide an update on the etiology, diagnostic methods and therapeutic strategies for the management of hyposalivation and xerostomia. The present paper describes subjective and objective methods for the diagnosis of salivary dysfunctions; moreover a number of drugs and systemic disorders associated with decreased salivary flow rate are listed. We also focused on the underlying mechanisms to radiotherapy-induced salivary damage. Therapeutics for hyposalivation and xerostomia were discussed and classified as preventive, symptomatic, topical and systemic stimulants, disease-modifying agents, and regenerative. New therapeutic modalities have been studied and involve stem cells transplantation, with special attention to regeneration of damage caused by ionizing radiation to the salivary glands. More studies in this area are needed to provide new perspectives in the treatment of patients with salivary dysfunctions.

Key words: salivary glands, xerostomia, radiotherapy, therapeutics, drug therapy.

INTRODUCTION

Saliva is of paramount importance for the maintenance of oral and general homeostasis. It displays a crucial role in the digestive function, taste, cleaning, hydratation of the oral mucosa, and protection of the teeth, due to buffering and remineralization properties.[1,2] Besides, saliva controls the composition of the oral

microflora due to antibacterial, antifungal and antiviral properties, protecting the body from deleterious extrinsic influences.[3-6]

Saliva is composed of more than 99% water along with electrolytes; the protein components include immunoglobulins, digestive enzymes such as amylase and lipase, and antibacterial and antifungal enzymes, as well as mucins.[1,2,7] Salivary secretion is controlled by the autonomous nervous system, mainly by parasympathetic nerve signals.[7,8] About 90% of saliva is produced by the major salivary glands[3,4] and the daily volume varies from 0.5 to 1.0 L.[6,8] When at rest, 65% of saliva is produced by the submandibular glands, which produce saliva rich in mucin, which supplies lubrification for the mucosa.[2,7,9] Under stimulation, the parotids account for 50% of salivary volume.[7-9]

Nederfors[10] suggests that salivary dysfunctions can be divided into three aspects: xerostomia, as subjective alteration; hyposalivation, as objective reduction of salivary flow and alterations in salivary composition. In early stages, hyposalivation is characterized by decreased salivary volume, besides saliva is thick and dispersed. The oral mucosa becomes dry and atrophic, and the patients can gradually show dysgeusia, dysphagia and dysphonia, as well as risk of developing ulcerations[4,6], caries, gingivitis, periodontitis, candidosis, and bacterial sialadenitis, among others.[11,12] Those changes cause important harm to the oral homeostasis and to the quality of life. Considering the abovementioned, the present study was designed to provide an update on the etiology, diagnostic methods and therapeutic strategies for the management of hyposalivation and xerostomia.

DIAGNOSIS OF SALIVARY DYSFUNCTIONS

The diagnosis of salivary dysfunctions can be obtained by means of subjective and objective methods. These methods can be classified into questionnaires or interviews, secretion tests, mucosal surface tests, qualitative analyses, functional analyses and glandular morphology analyses[13] (Table 1).

Table 1. Diagnostic methods of salivary dysfunctions.

Subjective analysis	Questionnaires or interviews	Questionnaires on xerostomia Visual analogue scale OHIP-14* QoL H&N35**
Objective analysis	Secretion tests	Sialometry Schirmer oral test
	Mucosal surface tests	Biopsies Salivary Ferning test Mucus®
	Functional analyses	Scintigraphy Wafer test
	Sialochemistry	Salivary composition test Total protein test
	Glandular morphological analyses	Sialography Ultrasonography Magnetic resonance Computed tomography

* Oral Health Impact Profile -14
****** Quality of Life Head and Neck 35
Source: Modified from Löfgren et al.[13]

Subjective methods are used to determine the intensity and cause of xerostomia.[14,15] A number of questionnaires have been utilized, and there is not a consensus on the best form of grading xerostomia, mainly due to the difficulty in obtaining a suitable response from the patient. Pai et al.[16] and Gerdin et al.[17] suggest the application of the visual analogue scale adapted to the evaluation of xerostomia.

Other authors suggest instruments that broaden the analysis of xerostomia, in grading aspects related to chewing, swallowing, speech, sleep and quality of life.[18]

The clinical method most often employed for the diagnosis of salivary dysfunction is sialometry, which consists in the whole saliva collection or the fluid produced by each major gland individually. Sialometry can be done by different methods, under stimulation or at rest.[13] Hyposalivation is considered when salivary flow rate (SFR) is < 0.1 mL/min at rest or < 0.7 mL/min under stimulation.[11,13] Otherwise, there are authors who consider SFR ≤ 0.3 mL/min, at rest, as abnormal.[19] Sialometry provides objective evidence of the reduction in SFR, but it does not help to diagnosis the dysfunction etiology.[4] The Schirmer test is usually employed in the diagnosis of xerophthalmia. Authors suggest its utilization also for quantifying non-stimulated SFR, since it consists in a simple method that provides an adequate diagnosis of glandular function. [20,21]

The assessment methods for the mucosal surface include biopsy of the minor salivary glands, the salivary ferning test and the *mucus*® test among others. The biopsy of the lower lip glands is used for the diagnosis of systemic disorders such as amyloidosis, sarcoidosis, Sjögren syndrome and neonatal hemochromatosis.[22] In the ferning test, hyposalivation is detected by electron microscopy, which evaluates the salivary crystals.[23] The *mucus*® test is a noninvasive method which analysis mucosal surface by a condenser that measures impedance with sensitive capacitors.[24]

Qualitative analysis of saliva includes assaying inorganic and organic components.[25-27] Diagnostic imaging techniques allow the identification of alterations in anatomic characteristics, as well as the evaluation of glandular function.[28] Salivary scintigraphy provides information about parenchyma and excretion of major salivary glands after endovenous administration of technetium pertechnetate.[29,30] It is a

noninvasive, easy to perform, reproducible technique and well tolerated by patients.[31] Like scintigraphy, the wafer test is a semiquantitative functional analysis method, employed in the initial diagnosis of salivary gland disorders.[19]

Magnetic resonance (MR) provides excellent image contrast for soft tissues and spatial definition, with the advantage of not using ionizing radiation.[32,33] In sialography by MR, the saliva itself serves as contrast in obtaining the images.[28] Its disadvantages include poor availability, high cost and time-consuming. Computed tomography (CT) is more accessible when compared to MR. It is indicated for the diagnosis of calculi inside the gland or duct and evaluation of bone erosion caused by malignant lesions.[32] The addition of radiodrugs allows the differentiation between benign and malignant lesions. It is the examination of choice in the diagnosis of inflammatory lesions of the salivary glands, but the patient is subjected to ionizing radiation with contrast.

Alternatively, ultrasonography is an easy to perform method with low cost. It enables to differentiate between intra- and extraglandular lesions, as well as between cystic and solid lesions, besides to diagnose calculi and dilations of salivary ducts, and to guide biopsies or drainages.[34]

ETIOLOGY OF SALIVARY DYSFUNCTIONS

DRUGS

More than 500 drugs are able of inducing hyposalivation and xerostomia, but they rarely cause irreversible damage to the salivary glands.[15,35] These drugs cause salivary dysfunction through anticholinergic, sympathomimetic, antimuscarinic,

cytotoxic action or by perturbating the ion transport pathways in the acinar cells[36,37] (Table 2).

Table 2. Drugs that cause salivary dysfunctions.

Drug	Subclass	Commercial form
Sympathomimetic drugs		
Antidepressant	-Monoaminoxidase inhibitors -Serotonin uptake inhibitors	Venlafaxine Reboxetine Fluoxetine HCl Maprotiline HCl
Antihypertensive	- Angiotensin converting enzyme Inhibitors - Angiotensin II receptor antagonists - Adrenergic blockers -Central adrenergic stimulants -Beta blockers -Calcium channel blockers	Metoprolol Monoxidine Rilmenedine Captopril Losartan Guanethidine Methyldopa Esmolol Felodipine
Appetite suppressors		Sibutramine Fenfluramine Phentermine
Decongestants		Pseudoephedrine Cetirizine Loratadine
Bronchodilators		Tiotropium
Skeletal muscle relaxants		Tizanidine
Antimigraine agents		Rizatriptain
Anticholinergic drugs		
Tricyclic antidepressants		Amitriptyline Clomipramine Amoxapine Protriptyline Doxepin Imipramine Trimipramine
Diuretics		Furosemide Bumetanide Torsemide

Table 2. Drugs that cause salivary dysfunctions.

		Ethacrynic acid
Muscarinic receptor antagonists		
Antipsychotics	-Haloperidol -Phenothiazine derivatives -Antiparkinsonian drugs -Anticonvulsivants	Promazine Triflupromazine Mesoridazine Thioridazine Clozapine Olanzapine
Antihistamines		Azatadine Brompheniramine Chlorpheniramine Cyproheptadine Dexchlorpheniramine Hydroxyzine Phenindamine
Cytotoxic drugs	-Antineoplastics	Fluorouracil Interferon Radioactive iodine
Drugs with unknown mechanism of action	- Proton pump inhibitors -Antimicrobials	Omeprazole Metronidazol Amoxicillin
Drugs with synergistic mechanism of action	-Opioids -Hypnotics	Tramadol Diazepam Lorazepam Alprazolam Lexotan

SOURCE: Modified from Sreebny and Schwartz[37] and Tschoppe et al.[38]

AGING

Several studies have investigated the effects of aging on the salivary glands, but there is still controversy as to the salivary dysfunctions in the elderly. While some authors have demonstrated impaired glandular function, others have not found salivary dysfunctions in the healthy and non-users of drugs elderly.[39-44] According to

Tylenda et al.[43], aging leads to the loss of about 30% of acinar cells, with substitution of secretory components by fibrous and adipose tissue.

Ghezzi and Ship[44] found that after the use of an anticolinergic drug, glandular function is more affected in the elderly than in young individuals. Besides, there are changes in salivary levels of sodium, potassium, IgA, proline-rich protein, lactoferrin and lysozyme in elderly.[1,2,45-48] Yeh et al.[49] identified a reduction in the SFR of elderly, even those not using systemic drugs, suggesting a relation between salivary dysfunction and aging.

On the other hand, there are authors that defend the hypothesis that the decrease of SFR in elderly results exclusively from the action of drugs and systemic disorders, more common in this age group than in young individuals.[50-51] According to Locker[50] and Shetty et al.[51] xerostomia is proportional to the number of drugs that the elderly utilize.

SYSTEMIC DISORDERS

Qualitative and quantitative salivary changes can be associated with particular systemic disorders that cause dysfunctions in neurotransmitter receptors, destruction of glandular parenchyma, interference with the secretion process or alterations in fluids and electrolytes.[42] Main systemic disorders related to glandular dysfunctions are listed in Table 3. Since many systemic conditions are associated with hyposalivation and xerostomia, it would not be possible to address them individually, and therefore, we chose to describe Sjögren syndrome, HIV infection and graft-versus-host disease.

Table 3. Systemic disorders associated with salivary dysfunctions.

Rheumatological Chronic Inflammatory Disorders	- Sjögren Syndrome - Rheumatoid Arthritis - Juvenile Idiopathic Arthritis - Systemic Lupus Erythematosus - Systemic Sclerosis - Primary Biliary Cirrhosis - Mixed Connective Tissue Disease - Sarcoidosis - Amyloidosis - Crohn's Disease - Ulcerative Colitis
Endocrine Disorders	- Diabetes Mellitus - Hyperthyroidism/Hypothyroidism - Cushing Syndrome - Addison's Disease
Neurologic Disorders	- Depression - Narcolepsy - Parkinson's Disease - Bell's Paralysis - Alzheimer's Disease - Holmes-Adie Syndrome
Genetic, Congenital or Chronic Disorders	- Agenesis of Salivary Glands - Ectodermic Dysplasia - Cystic Fibrosis - Prader-Willi Syndrome - Auto-Immune Thyroiditis - Chronic Pancreatitis - Celiac Disease - Down Syndrome - Familial Amyloidotic Polyneuropathy - Myotonic Dystrophy - Gaucher Disease - Major Thalassemia - Papillon-Lefèvre Syndrome
Metabolic Disorders	- Dehydration - Eating Disorders - End Stage Renal Disease - Nutritional Deficiencies - Anorexia Nervosa - Bulimia - Anemia - Atrophic Gastritis - Alcohol Abuse
Infectious Disorders	- HIV/AIDS - Epidemic Parotitis - Epstein-Barr Virus Infection - Bacterial Sialadenitis - Tuberculosis
Others	- Hemochromatosis - Wegener's Disease - Hypertension - Fibromyalgia - Chronic Fatigue Syndrome

Source: Porter et al.[4]; von Bultzingslowen et al.[42]

Sjögren Syndrome

One of the disorders most associated with hyposalivation is Sjögren syndrome, an autoimmune disease of unknown etiology that affects the exocrine glands, mainly the salivary and lacrimal glands.[20] The disease may include impaired pulmonary, articular, renal and neurological function in its spectrum.[52,53] The syndrome is classified as primary when limited to the exocrine glands, and secondary if accompanied by other autoimmune diseases.[54,55] Its autoimmune profile is due to the circulating antibodies and glandular lymphocytic infiltrate, composed mainly of TCD4 lymphocytes.[20,56,57] Evidence indicates that the severity of secretory dysfunction is not necessarily related to the degree of glandular infiltration and destruction.[22]

The treatment of extraglandular manifestations of the disease includes drugs such as hydroxychloroquine, methotrexate and systemic corticosteroids, which appear to foster increased SFR.[54,58] The monoclonal antibodies rituximab and epratuzumab have been shown to be effective in reducing glandular inflammation, alleviating xerostomia and increasing SFR.[59,60]

HIV Infection

Between 2 and 10% of patients infected by HIV present with xerostomia and up to 37% reduction in SFR.[61,62] The principal causes of dysfunction are disease of the salivary glands associated with HIV, Kaposi sarcoma, non-Hodgkin lymphoma, intraglandular lymphadenopathy and acute suppurative sialadenitis.[4] Glandular involvement is more common in children, who also show more favorable therapeutic

results than do adults. The outcome of anti-retroviral treatments has led to a decrease in the prevalence of these alterations.[63] Xerostomia in HIV-positive patients can also be the consequence of drugs such as didanosine, reverse transcriptase inhibitors or proteases.[4]

Graft-versus-host disease

Graft-versus-host disease is an association of clinical alterations that appear after bone marrow transplantation.[64,65] The disease is mediated by autoreactive T lymphocytes which infiltrate several tissues and organs.[66] The disease shows different degrees of morbidity, with cutaneous, oral, ophthalmologic, pulmonary, articular and genitourinary manifestations. In the oral mucosa, there are lichenoid lesions, erythema, ulcerations, and areas of hyperkeratosis and atrophy.[67] Xerostomia is the result of fibrosis of the parotid glands and alterations in the chemical composition of saliva, with decreased levels of sodium and increased potassium. In the chronic course of the disease, the muscarinic receptors are harmed.[68]

RADIOTHERAPY AND CHEMOTHERAPY

The major salivary glands are often involved in the radiation portals because they are in the proximity of the primary tumor sites and lymphatic chains of the head and neck region. As a consequence of radiotherapy, they undergo a process of degeneration, resulting in hyposalivation and xerostomia.[69] The severity of dysfunction is determined by factors such as dose, radiation portals and individual

response of the patient.[70,71] In malignant tumors located in the posterior portion of the mouth and in the oropharynx, radiotherapy includes parallel and opposing lateral fields on the upper region of the neck and side of the face. In these cases, both parotids are irradiated, leading to greater levels of xerostomia.[72,73]

Radiotherapy-induced hyposalivation ranges from a small degree of dry mouth to total lack of saliva and oral mucosa atrophy. The saliva undergoes qualitative alterations, there are decreased activity of amylases, buffering capacity and pH, with consequent acidification.[74] There are also increased levels of calcium, chloride, magnesium and proteins and reduction in bicarbonate.[75] These alterations indicate that the parotids function is more affected than that of the other glands.[76] Eisbruch et al.[69] suggested that on the radiotherapy the decrease in SFR can be related to development of mucositis, which occurs due to reduction in mucins, and epidermal and fibroblast growth factors.

Damage to the acinar cells becomes irreversible after cumulative doses of 26 to 39 Gy, causing the patients to have a SFR less than 10% of that prior to radiotherapy.[77,78] Xerostomia is perceived in the initial phases of radiotherapy, with reductions of 50 to 60% in SFR in the first week, and up to about 80% at the end of the seventh week.[79,80]

Despite being stable, because they do not have a high mitotic rate, acinar cells respond readly to radiation.[81] The mechanisms that lead to tissue destruction and greater sensitivity of salivary glands are still inconclusive.[81,82] The glandular alterations begin with damage to the plasma membrane, loss of response to autonomic control, edema, degeneration and necrosis of acinar cells. The acute effects begin 24 hours after the start of therapy and stabilize in 72 hours. The late effects are a consequence of fibrosis and acinar atrophy[12,83], which occur because of

mesenchymal alterations, including changes in the extracellular matrix, especially laminin and collagen IV.[84]

Hakim et al.[85] evaluated, in the parotids of rabbits, functional changes and Ki67, smooth muscle actin (SMA) and tenascin-C immunodetection after irradiation with 15 Gy. There was a significant change in the absorption of ^{99m}Tc-pertechnetate, decreased Ki67detection and marked redistributions of SMA and tenascin-C. According to the authors, the increased tenascin-C detection, caused by the damage to the basal membrane of acinar cells, and the reduction in SMA expression can be responsible for the functional glandular changes.

Avila et al.[86] demonstrated that ionizing radiation induced apoptosis in the acinar cells of the parotids of rodents. Apoptosis induced by radiation was dose-dependent and was correlated with salivary dysfunctions. In addition, the apoptotic response seen after irradiation was dependent on p53 expression. Cannon et al.[87] demonstrated radiotherapy toxicity to the parotid gland by means of fluorodeoxyglucose-labeled positron emission tomography-computed tomography (FDG-PET-CT).

The alterations in SFR and viscosity can persist for years and recovery depends on the characteristics of each patient.[74] Currently, with the use of intensity-modulated radiotherapy (IMRT), the tissues located in the proximity of the tumor are more preserved in comparison with conventional radiotherapy.[88] IMRT is a technique that allows radiation to be dosed and distributed in the tumor more precisely, thereby sparing surrounding tissues.[89]

Exclusive chemotherapy treatment causes transient xerostomia, with recovery of salivary levels as prior to treatment one year after the end of treatment cycles.[90] According to Jensen et al.[90], chemotherapeutic drugs appear to affect the function of

acinar and ductal cells, by influencing cell division. Chemotherapeutic agents can induce dilation of the excretory duct, acinar degeneration and inflammation of glandular tissue.[91]

THERAPEUTIC OPTIONS

The therapeutic approach of salivary dysfunctions depends basically on residual glandular function and is aimed at the alleviation of symptoms and prevention and correction of eventual sequelae, as well as at the treatment of associated systemic diseases. The treatment of hyposalivation and xerostomia can be classified as (1) preventive, (2) symptomatic, (3) topical and systemic stimulants, (4) disease-modifying agents, and (5) regenerative.[42,92]

PREVENTIVE THERAPIES

Cytoprotective drugs, used to minimizing the effects of radiotherapy, have been studied. Amifostine is an organic thiophosphate utilized in patients subjected to high doses of ionizing radiation, whose portal includes a large part of the parotids.[93] Its protective effect prevents the formation of free radicals and provides DNA repair, reducing the intensity and duration of xerostomia, without interfering with the control of the tumor and patients survival.[94] Despite these benefits, amifostine has adverse effects such as nausea, vomiting, hypotension, transient hypocalcemia and allergic reactions.[95] Another cytoprotector described in the literature is tempol, a stable nitroxide that still needs clinical studies to support its use in humans.[77] Cotrim et al.[96] demonstrated that tempol maintained normal SFR in irradiated animals.

The insulin-like growth factor and keratinocyte growth factor (KGF) in animals suppress apoptosis and favor the survival and proliferation of acinar cells after radiotherapy.[97,98] Zheng et al.[99] demonstrated that KGF prevented hyposalivation in mice, since the transgenic animals showed a higher number of acinar and endothelial cells.

Teymoortash et al.[100] suggested the utilization of botulinum toxin as an alternative preventive against salivary damage caused by ionizing radiation. The intraglandular application of the toxin, prior to radiotherapy, significantly prevented functional and histological changes in rats.

In irradiated patients, the transfer of the submandibular gland to the submental space is also indicated as a preventive method. The transfer allows the structure to receive a lower quantity of radiation, therefy maintaining its excretory function.[101]

Some preclinical studies of genetic transfer for glandular protection have been conducted. Baum et al.[102] and Delporte et al.[103] in studying human aquaporin-1 (hAQP1) in animals, observed that its action on the salivary glands causes an increase in aqueous secretion in response to an osmotic gradient. Currently, a phase I study was done in patients to evaluate its safety in humans.[104] Another study indicated positive results with use of manganese superoxide dismutase-plasmid/liposomes (MnSOD-PL) in the prevention of the noxious effects of ionizing radiation on the salivary glands.[105] Palaniyandi et al.[106] identified a splice variant of a cellular kinase, Tousled-like kinase 1B (TLK1B), which when overexpressed protected normal epithelial cells against ionizing radiation-induced cell death. The results demonstrated a reduction in acinar atrophy, glandular fibrosis and inflammatory infiltrate.

DISEASE-MODIFYING AGENTS

Disease-modifying agents especially include immunomodulatory and immunosuppressive drugs, utilized in patients with Sjögren syndrome, with the objective of reestablishing the altered immunologic mechanisms.[20] Interferons are proteins that regulate cell proliferation and differentiation, cellular expression of surface antigens and induce enzymes.[22] The results with respect to the use of interferon alpha for xerostomia are controversial. Ferraccioli et al.[107] found that parenteral administration of interferon alpha-2 three times a week produced an increase in salivary and lachrymal secretions. Ship et al.[108] observed that this drug enhanced SFR under stimulation but did not alter flow at rest. On the other hand, Cummins et al.[109] found considerable elevation in SFR at rest and small alteration in stimulated SFR.

Another disease-modifying agent is rituximab, a monoclonal antibody that crossreacts with the antigen CD20, present in more than 90% of B cells. Its benefit with regard to xerostomia is related to reducing glandular lymphocytic infiltrate occurring in Sjögren syndrome.[60]

SYMPTOMATIC THERAPIES

Drinking water frequently is an alternative more commonly used by patients with xerostomia, but saliva substitutes can provide higher viscosity and protection to the oral mucosa.[77] The ideal agent should provide long-lasting and intense hydration of the oral mucosa, requiring a minimal number of applications, without adverse

effects.[6] Saliva substitutes differ in chemical composition and viscosity.[110] They are mostly composed of carboxymethylcellulose (CMC), mucins, xanthan gum, hydroxyethylcellulose, linseed oil or polyethylene oxide.[77,110] When lubricants containing CMC are compared to those with mucins and xanthan gum, their rheologic and moisturizing properties are inferior.[111] Gelatinous substitutes of saliva, containing polyglycerylmethacrylate has also been suggested and are indicated for periods of decreased SFR.[112] According to Dost and Farah[113], the length of salivary substitutes tends to be limited and there is a need for frequent reapplication.

Other symptomatic strategies include the slow release and continuous oral lubrication mechanisms.[114] Tsibouklis et al.[115] cite hydrogel films that allow the continuous release of substances for treatment of xerostomia. However, these can interfere with speech in patients.[116]

TOPICAL AND SYSTEMIC STIMULANTS

Pilocarpine is a parasympathomimetic, non-selective muscarinic agonist, which has been indicated for the treatment of xerostomia. Its recommended initial dose is 5 mg/day up to a maximum of 30 mg/day.[117] In patients subjected to radiotherapy of the head and neck, the maximal effect of pilocarpine is obtained between two and three months after the start of treatment.[118] Its adverse effects include hyperhidrosis, nausea, rhinitis, dizziness, intestinal colic and polakuria. Its use is contraindicated in heart patients, individuals with chronic obstructive pulmonary disease, asthma and glaucoma.[119]. Epstein and Schubert[120] proposed the association of pilocarpine and anethole trithione (ANTT) to potentiate the effect of both on the salivay function. ANTT does not have a cholinergic action, but increases

the availability of muscarinic receptors in the post-synaptic membrane.[121,122] However, this association did not demonstrate positive results in the treatment of xerostomia in patients with primary Sjögren syndrome.[123]

Cevimeline is a selective muscarinic agonist for M1 and M3 receptors, found in the salivary and lacrimal glands. Since it has no effect on M2 receptors, it shows fewer adverse effects when compared to pilocarpine, and besides, it has a long-lasting action. The most common associated side effect is dyspepsia.[124] The recommended dose is 30 mg administered three times a day.[125]

Another systemic sialogogue is bethanecol, a carbamic ester of β-methylcholine resistant to cholinesterase, whose action is concentrated in the M3 receptors. Jham et al.[126], in a randomized phase III trial, observed a significant increase in SFR at rest and a decrease in xerostomia in patients treated with head and neck radiotherapy. The dose indicated is 25 mg, three times a day. Its adverse effects, despite being infrequent, include nausea and diarrhea.

To stimulate salivary secretion, other drugs such as bromhexine[127,128] and nizatidine[129,130] are described in the literature. Bromhexine is a drug with mucolytic properties, used in respiratory infections, which also enhances salivary and lachrymal secretion. Nizatidine is an H2 receptor antagonist which inhibits acetylcholinesterase, allowing a greater availability of acetylcholine. Both have shown favorable results in SFR and have been used in patients with Sjögren syndrome.[127-130]

Sugar-free chewing gum and jellybeans can be utilized as topical salivary stimulants.[92] They usually contain xylitol (low calorie sugar), which inhibits the growth of cariogenic bacteria and reduces the incidence of caries.[131] Kleinegger[132] describes SalivaSure® as a topical stimulant that does not irritate soft tissues or cause tooth decay. Its composition includes citric acid and xylitol.

Domingo[133] utilized electrostimulation in patients with salivary dysfunction, and obtained an increased SFR from parotids. Meanwhile, the results with this technique are still inconclusive.[134] Acupunture is also cited as an alternative for xerostomia. Subjective and objective aspects of salivary function are improved with those technique.[135,136]

In addition to this, hyperbaric oxygen in irradiated patients demonstrates increased salivary function[137] and reduction in the number of cariogenic bacteria and *Candida albicans.* Teguh et al.[138] pointed out that hyperbaric oxygen favors neoangiogenesis and recruitment of bone marrow stem cells.

REGENERATIVE THERAPIES

Stem cell transplantation is emerging as an alternative for the reestablishment of glandular function, since these cells have the capacity to self-renew and differentiate into any type cell constituent of the salivary glands.[139-141] Bone marrow stem cells and adipose tissue-derived stromal cells have been tested.[142-145] Yamamura et al.[146] suggested the utilization of dental pulp cells as a form of treatment for hyposalivation after radiotherapy.

DISCUSSION

Salivary dysfunctions are common, have a negative impact on the quality of life, and can be caused by a number of local and systemic conditions. Clinicians must be aware of the signs and symptoms of salivary disorders and be able to diagnose and treat them. In this review, we described subjective methods, as well as objective

methods for determining alterations in salivary secretion. In addition to this, we addressed the possible etiologic factors and established treatments in the literature, as well as new therapeutic strategies still under investigation.

The use of medications is the most frequent cause of xerostomia[4,37,38], because a number of drugs are associated with salivary dysfunctions. Triccyclic antidepressants, sedatives, tranquilizers, antihistamines, antihypertensives and anticonvulsants are examples of often used drugs that are associated with salivary hypofunction.[4,37] Besides drugs, changes related to aging[43-49] and a number of systemic disorders[4,42,56,61,68], such as Sjögren syndrome, are associated with decreased SFR.

Another important factor associated with salivary dysfunction is radiotherapy. Approximately 70% of patients who receive radiotherapy of the head and neck develop hyposialia, due to a progressive decrease in salivary gland function.[69-72] There is macroscopically detectable loss of glandular structure as a consequence of radiotherapy, besides microscopic alterations indicative of cell death, hypovascularization, formation of fibrous tissue and edema.[81-86] In these cases, preventive therapies such as submandibular gland transfer and the use of cytoprotective agents, growth factors and botulinum toxin have been tested for minimizing the effects of ionizing radiation on the salivary glands.[93,96-101]

The treatment of salivary dysfunctions is mainly devoted to alleviate symptoms and to stimulate residual glandular function. The symptomatic treatments consist mainly in salivary substitutes, which provide continuous lubrication of the oral mucosa[6,77,11-113]. Currently, devices for slow and prolonged release of these oral lubricants, mimicking glandular function, have been tested.[114-116] In relation to salivary stimulation methods, current interest is focused on the development of drugs

that increase SFR without adverse effects. Such drugs have not yet been found, although the use of pilocarpine, cevimeline and bethanechol has been established. [119,120,124,126]

Clinicians, together with the patient, should select a therapeutic modality most suited for each case. The patient must be informed about the etiologic factors and adverse effects of hyposalivation, instructed about oral hygiene, drinking water frequently (to maintain the mucosa hydrated) and to avoid spicy and containing sugar foods, caffeine or alcohol.[36] New therapeutic modalities have been studied and involve stem cells transplantation[140-146], with special attention to regeneration of damage caused by ionizing radiation to the salivary glands. More studies in this area are needed to provide new perspectives in the treatment of patients with salivary dysfunctions.

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4 ARTIGO DE PESQUISA

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EFFECT OF LOW-LEVEL LASER THERAPY ON RADIOTHERAPY-INDUCED HYPOSALIVATION AND XEROSTOMIA: A PILOT STUDY

Artigo submetido para avaliação (Anexo F)

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EFFECT OF LOW-LEVEL LASER THERAPY ON RADIOTHERAPY-INDUCED HYPOSALIVATION AND XEROSTOMIA: A PILOT STUDY

LLLT on radiotherapy-induced salivary dysfunction

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ABSTRACT

Objective: The present pilot study aimed to assess the effect of low level laser therapy (LLLT) on hyposalivation and xerostomia due to head and neck radiotherapy. **Background:** Major salivary glands are commonly involved at the radiation sites as they are close to the primary tumor and lymph chain in the head and neck region. As a consequence of the radiotherapy, they go through a degenerative process which results in salivary hypofunction. **Methods:** Twenty three patients with a history of head and neck malignancy and treated by fractioned teletherapy (dosimetry ranging from 45 to 70 Gy), whose therapeutic site had involved at least 50% of the major salivary glands were selected. Patients were randomly distributed into laser group (n=12) and control group (n=11). A AsAlGa laser was used punctually in the major salivary glands, twice a week for six weeks, with a 12-session total. Stimulated and unstimulated salivary flow rate (SFR) was assessed, as well as the xerostomia and quality of life related to oral health (QLROH). **Results:** Analysis has not shown any significant difference between the groups with regards to the SFR and xerostomia, and the QLROH. However, at the end of the treatment, the xerostomia and the QLROH showed significant improvement in both groups compared to assessments carried out in baseline, highlighting the importance of advice given to the irradiated patients and their follow-up. **Conclusion:** In the parameters used, LLLT was not able to increase SFR or decrease xerostomia. The results may be associated to the late effects of radiotherapy on glandular structure such as fibrosis and acinar atrophy.

Key Words: low-level laser therapy, head and neck cancer, radiotherapy, phototherapy.

INTRODUCTION

The major salivary glands are commonly involved at the radiation sites as they are close to primary tumor and lymph chains of the head and neck region. As a consequence of radiotherapy they go through a degenerative process resulting in hyposalivation and xerostomia.[1] Approximately 70% of the irradiated patients have developed such alterations[2], with several complications, such as total or partial loss of taste, mouth burning and pain, susceptibility to oral ulcerations, cavities and other infections, dysphagia and dysphonia and even psychological alterations that negatively influence their quality of life.[3]

The dose of ionizing radiation, amount of salivary tissue exposed and patient's individual response are the main factors influencing glandular alterations.[4-6] Damage becomes irreversible after cumulative doses ranging from 26 to 39 Gy, and the salivary flow rate (SFR) can get under 10% from the one presented before radiation.[7,8] Despite being stable, as they do not have high mitotic rates, acinar cells respond quickly to radiation.[9,10] The mechanisms that lead to tissue destruction and salivary glands radiosensitivity have not been totally understood so far. Salivary gland alterations start with the damage to the plasmatic membrane, with loss of response to the autonomic controls, and progression to edema, degeneration and acinar cell apoptosis. Acute effects start 24 hours after therapy starts and stabilize within 72 hours. Late effects are the consequence of fibrosis and acinar atrophy[11,12], which occur due to mesenchymal alterations, including changes in the extra cellular matrix, specifically in the lamilin and in collagen IV. [13,14]

Low level laser therapy (LLLT) is a simple low cost tool that can be used as an adjuvant to conventional treatments, or alone and electively in some diseases.[15-18] Its

effects are based on the modulation of several metabolic, biochemical and photophysical processes that transform laser light into useful energy for the cell. The LLLT effect on xerostomia has been investigated in clinical and pre-clinical studies.[16,17,19,20] Simões et al.[16] demonstrated that LLLT increased the SFR and the levels of salivary proteins in Wistar rats. In patients irradiated in the head and neck region, Lopes et al.[19] and Simões et al.[20] showed that LLLT decreased xerostomia and increased stimulated SFR.

The objective of the present pilot study was to clinically assess LLLT effect on radiotherapy-induced hyposalivation and xerostomia. Besides, the influence of this therapeutic modality on the quality of life related to oral health was also assessed.

PATIENTS AND METHODS

Fifty-one patients treated with radiotherapy in head and neck region were assessed consecutively; these patients came from Rio Grande do Sul State Radiotherapy Services, Brazil (São Lucas Hospital - Pontifical Catholic University of Rio Grande do Sul, Santa Casa Hospital Complex, Bruno Born Hospital, Tacchini Hospital and Charity Hospital). From these, 23 individuals between 37 and 69 years old were selected; all with a history of head and neck malignacy, treated with ionizing radiation, through fractioned teletherapy, with dosimetry ranging from 45 to 70 Gy, whose therapeutic site had involved at least 50% of the major salivary glands (uni or bi-laterally). Patients should have been followed up for at least six months after radiotherapy (with no relapses or metastasis), present Karnofsky[21] performance scale higher or equal to 60, present xerostomia and hyposalivation (unstimulated salivary

flow rate below 0.1 mL/min and, under stimulation, below 0.7 mL/min). All the selected patients signed the Informed Consent Form.

The individuals were randomly distributed into laser group (n=12) and control group (n=11). All the patients received instructions regarding oral hygiene, mucosal hydration and were advised to avoid spicy and citric foods consumption, as well as alcoholic beverages and tobacco. The study flowchart is shown in figure 1.

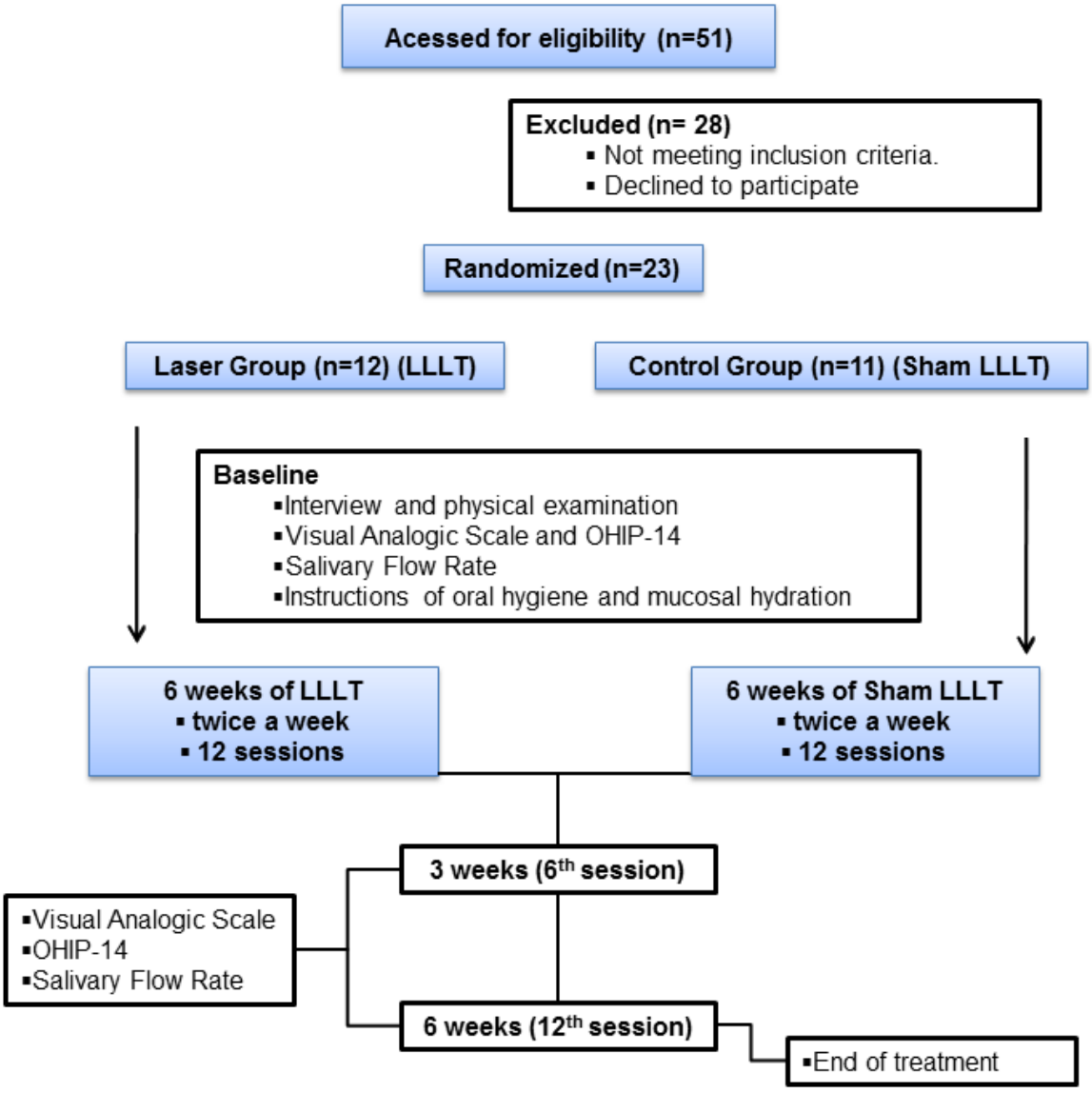

Figure 1. Flowchart representing the stages of the study.

Xerostomia and Salivary Flow Rate (SFR)

Visual Analogic Scale (VAS) developed by Pai et al.[22], consisting of eight items related to xerostomia and quantified by 10cm-long horizontal lines, was used for xerostomia assessment.

Stimulated and unstimulated whole SFR was determined. Samplings were collected in the morning, between 8:00 and 11:00 a.m., in previously weighed polypropylene vials. Patients were advised not to ingest food or drink, not to use cosmetics or drugs on the lips, and not to smoke or undergo physical stress one hour before the procedure. For unstimulated saliva sampling, patients were advised to keep their lips slightly open allowing saliva to run passively into a vial for 15 minutes. For stimulated salivary sampling a 1.0 cm long and 0.5 cm diameter latex cylinder held by dental floss was used. Stimulation was carried out for 5 minutes, and at each minute the content collected was deposited into the vial. The content of both samplings was weighed on a precision scale and transformed into mL/min.[23,24]

Xerostomia and SFR were assessed in baseline, after the sixth session and at the end of the 12th treatment session.

Quality of Life Related to Oral Health (QLROH)

The QLROH was assessed through the Oral Health Impact Profile (OHIP-14) questionnaire, Portuguese language version.[25] This instrument was also applied in baseline, after the sixth session and after the 12th treatment session.

Low Level Laser Therapy (LLLT)

A AsAlGa diode laser was used (Thera Lase® DMC Equipamentos Ltda., São Carlos, SP, Brazil) according to the following parameters: 830 nm (infrared)

wavelength, 100 mW power, continuous emissions, 2 J energy per point, application time 20 seconds per point. The area of the spot tip of this tool is 0.03 cm^2. Patients underwent two LLLT weekly sessions for six weeks, total of 12 sessions. Before each application the power of the tool was calibrated and then, checked by means of a power meter.

LLLT was carried out in the major salivary glands punctually. Three points were applied on each parotid gland, two on each submandibular and two on each sublingual gland[19]. The tip of the tool remained in contact with the patients' skin in the applications on the parotid and submandibular glands. On the points meant for the sublingual glands, the tip was placed on the floor of the mouth.

The same number of sessions and application protocol were carried out with the control group as with the laser group; however, the tool received a plastic tip with rubber interior that blocked radiation emission, which was confirmed by means of a power meter before the applications in the control group.

STATISTICAL ANALYSIS

Stimulated and unstimulated SFR, as well as the scores from the quality of life related to oral health (OHIP-14) were compared between the groups by the Mann-Whitney test. In each group, in order to compare the SFR and the quality of life scores obtained in baseline, after the LLLT 6^{th} and 12^{th} session, Friedman test was used complemented by its multiple comparison test. The VAS scores were assessed by using the repeated-measures analysis of variance (ANOVA) complemented by the Tukey multiple comparison test. Values $P \leq 0.05$ were considered significant.

RESULTS

Characterization of the sample

The demographic characteristics of the sample, the treatments for the malignancies, systemic alterations and drugs used during the study are shown in Table 1. The time between radiotherapy and the beginning of the study was about 46 months in the control group and 40 months in the laser group. Tobacco and alcohol had been used by 73.91% and 52.17% of the patients, respectively, up till the moment malignant neoplasia was diagnosed. At the time they were included in the study, all patients had already interrupted the use of those substances.

Table 1. Demographic distribution of the patients and characteristics of the treatment within the groups studied.

Characteristic	Laser Group n=12	Control Group n=11
Sex		
Male	6 (50%)	9 (81.81%)
Female	6 (50%)	2 (18.18%)
Age		
Range	44-69	37-66
Mean(±SD)	58.66 ±9.07	55.63 ±8.65
Treatment		
Radiotherapy + Chemotherapy	3 (25%)	3 (27.27%)
Radiotherapy + Surgery	4 (33.33%)	6 (54.54%)
Radiotherapy + Surgery + Chemotherapy	5 (41.66%)	2 (18.18%)
Submandibular Excision		
No	4 (33.33%)	3 (27.27%)
Both	2 (16.66%)	-
Right	4 (33.33%)	4 (36.36%)
Left	2 (16.66%)	4 (36.36%)
Systemic Disease		
No	4 (33.33%)	7 (63.63%)
Hipertension	5 (41.66%)	3 (27.27%)
Diabetes	2 (16.66%)	1 (9.09%)
Hypothyroidism	3 (25%)	1 (9.09%)
Other	2 (16.66%)	1 (9.09%)
Systemic Medications		
No	3 (25%)	6 (54.54%)
Thyroid Hormone	3 (25%)	1 (9.09%)
Analgesic	2 (16.66%)	-
Antihypertensive	1 (8.33%)	1 (9.09%)
Antilipidemic	2 (16.66%)	1 (9.09%)
Anti-diabetic	1 (8.33%)	1 (9.09%)
Antidepressants	1 (8.33%)	1 (9.09%)

Xerostomia and Salivary Flow Rate (SFR)

Xerostomia scores, which were assessed by VAS, presented no significant difference between the groups in both baseline, after the 6th session, or at the end of the treatment (12th session). However, both in the laser group and in the control group, there was a significant decrease in xerostomia at the end of the 12th session of the treatment if compared with the assessment carried out in baseline (Table 2).

The stimulated and unstimulated SFR did not differ significantly between the groups in baseline, after the 6th session, or at the end of the treatment (12th session). When comparing the SFR of each group at different experimental times, a significant increase in unstimulated SFR was observed at the end of the treatment in the control group (Table 3).

Table 2. Visual analogic scale (VAS) scores for xerostomia in the laser group and control group in baseline, after the 6th and 12th LLLT sessions.

Assessment	**Control Group n=11**		**Laser Group n=12**	
	Mean	DP	Mean	DP
Baseline	6.51^{A}	1.43	6.30^{A}	1.67
6th session	6.40^{A}	1.33	4.74^{A}	1.79
12th session	4.65^{B}	1.96	4.15^{B}	2.63

Means followed by different letters in the column differ significantly through ANOVA test, using repeated measurements design, complemented by Tukey multiple comparison test, with 5% significance level.

Table 3. Stimulated and unstimulated salivary flow rate (SFR) (mL/min) in the laser group and control group in baseline, after the 6th and 12th LLLT sessions.

SFR (mL/min)		Control-group n=11		Laser-group n=12		P*
		Median (P25 – P75)	Rank**	Median (P25 – P75)	Rank**	
Unstimulated	Baseline	0.025 (0.007 – 0.036)	1.64 ^{B}	0.013 (0.006 – 0.025)	1.75 ^{A}	0.347
	6th session	0.017 (0.014 – 0.043)	1.73 ^{AB}	0.016 (0.004 – 0.043)	2.08 ^{A}	0.608
	12th session	0.028 (0.013 – 0.055)	2.64 ^{A}	0.019 (0.009 – 0.046)	2.17 ^{A}	0.379
Stimulated	Baseline	0.111 (0.051 – 0.189)	2.09 ^{A}	0.063 (0.022 - 0.118)	1.75 ^{A}	0.288
	6th session	0.129 (0.078 – 0.217)	2.09 ^{A}	0.073 (0.023 – 0.169)	2.17 ^{A}	0.379
	12th session	0.110 (0.049 – 0.133)	1.82 ^{A}	0.103 (0.021 – 0.157)	2.08 ^{A}	0.695

* Comparison between groups: Mann-Whitney's test

** Comparison between times of the study: mean ranks followed by different letters in the column, differ significantly in the Friedman non-parametric test, complemented by its multiple comparison test, at a 5%significance level.

Quality of Life Related to Oral Health (QLROH)

The QLROH, assessed through OHIP-14, did not differ significantly between the groups in baseline, after the 6th session, or at the end of the treatment (12th session). Both in the laser group and the control group, there was a significant decrease in the OHIP-14 scores at the end of the treatment when compared to the assessment carried out in baseline (Table 4).

Table 4. Oral health impact profile (OHIP-14) scores for quality of life related to oral health assessment in the laser group and control group in baseline, after the 6th and 12th LLLT sessions.

OHIP-14	Control Group n=11	Laser Group n=12	P
	Median (P25 – P75)	Median (P25 – P75)	
Baseline	10.23^{A} (6.39 – 12.82)	10.48^{A} (6.82 – 14.00)	0.786
6th session	5.17^{B} (2.28 – 10.69)	7.55^{AB} (5.65 – 11.19)	0.413
12th session	3.53^{B} (0.66 – 10.44)	2.52^{B} (1.69 – 9.84)	0.976

Mann-Whitney's test significant at p≤0.05

DISCUSSION

The present pilot study has investigated the LLLT effect on hyposalivation and xerostomia in patients with head and neck malignancies treated with radiotherapy. All these selected patients presented important salivary dysfunction as a consequence of radiotherapy. Although the literature show, in pre-clinical and clinical studies, the benefits of LLLT in salivary flow increase[16,19,20,26-30], there is not any study investigating its effects on patients that have already ended radiotherapy and present hyposalivation and xerostomia as a sequela.

Low level laser radiation is a non-ionizing and non-invasive form of radiation, well tolerated by the tissues and with no mutagenic effects. LLLT effects on salivary glands have not been completely understood so far. Studies have shown an increase in the number of duct epithelial cell mitosis, and stimulation to protein synthesis in submandibular glands of rats.[26,31]. As a result of mitochondria stimulation, increase in ATP levels, increase in glucose consumption by the cells, and the intracellular calcium level, LLLT can promote cell proliferation, increase in the anti-apoptotic protein expression as well as in blood micro-circulation in the salivary glands.[19,29,32,33] However, the present study has not confirmed the hypothesis that LLLT could stimulate residual gland function in patients submitted to head and neck radiotherapy. No significant difference was observed between laser and control groups regarding the SFR and OHIP-14 scores and VAS. When using LLLT in head and neck radiated patients, Cowen et al.[34], Lopes et al.[19], Simões et al.[20] and Oton-leite et al.[30] observed decrease in xerostomia and increase in the SFR, suggesting lasertherapy as an adjuvant in the treatment of salivary alterations due to radiotherapy. However, in those studies, the LLLT was applied concurrently to

radiotherapy, i.e., when irreversible morphological alterations such as, acinar athrophy and fibrosis had not been produced in the major salivary glands yet. In contrast, in the present study pilot, patients had ended radiotherapy for at least six months thus, the negative results obtained with regards to LLLT, can be attributed to late alterations due to ionizing radiation in the glandular structure. All patients had received ionizing radiation doses ranging from 45 to 70 Gy, which several authors[35-37] consider irreversible for glandular function restoration.

At the end of the treatment, however, there was a decrease in xerostomia and a improvement in the QLROH in both groups. It is important to highlight that all patients were advised, early in the experiment, about the importance of oral mucosa hydration, dental hygiene care and frequent stimulus of the salivary glands. Those recommendations were reinforced in each of the 12 sessions regardless of the group the patient was in. The assistance to the individuals, carried out during the six weeks of the study, was the determining factor for the improvement of xerostomia and QLROH, showing the need of a follow-up for the head and neck irradiated patients, in order to manage the sequelae caused by radiotherapy. Decrease in xerostomia was not followed by a clinically significant increase in the amount of saliva. Dawes[38] and Jensen et al.[39] suggest that xerostomia does not necessarily present correlation with the SFR. Bhide et al.[40] mention that the difference between the patient perception and the salivary flow could suffer from the influence of external factors.

Although there was no difference in the SFR between the laser and control groups, a significant increase in the unstimulated SFR was observed in the control group at the end of the experiment, in relation to the baseline assessment. With regards to the stimulated whole saliva, the values obtained at the end of the study did not differ from the baseline values in both groups. The result of the unstimulated SFR

in the control group, in spite of being statistically significant, did not have any clinical significance once the values were much below what is considered normal. The median of the unstimulated SFR in that group was 0.028 mL/min at the end of the study, while the normal value is 0.1 mL/min. During randomization of the sample, the laser group presented two patients with bilateral neck dissection and excision of both submandibular glands, while the control group did not have patients in such condition. Taking into consideration that the submandibular glands supply two thirds of unstimulated whole saliva, that factor might have justified the difference in unstimulated SFR in the control group.

The lack of an LLLT therapeutic protocol made these study methodological definitions difficult. In the literature, the power, power density, wave length, and all other parameters differ considerably in the studies that used LLLT for xerostomia treatment.[19,20] We have opted for using the infrared wave length due to the depth of the glandular parenchyma to be irradiated[17]. The frequency of the sessions in the other studies ranged from once a week[20] to daily applications[19]. In our study the sessions were carried out twice a week for six weeks with the objective of keeping a steady cell response. Furthermore, as some authors mention that LLLT can stimulate not only the healthy cells but also the tumor cells.[41-43] Hence, during LLLT applications, the areas close to the already treated tumor lesions were avoided.

As xerostomia has serious consequences on the patients quality of life, we have opted for assessing the QLROH, using the OHIP-14. Nowadays, several tools are available for that purpose, not a single one considered gold-standard[44], though. Taking into account the decrease in the OHIP-14 scores along the six-week-study, the relation between xerostomia relief perception and improvement in the quality of life of the individuals in the research is evident.

Saliva plays an important role in the oral and general homeostasis, once salivary dysfunctions predispose individuals to several complications. Radiotherapy carried out in the head and neck region is one of the main causes of salivary disorders, interfering negatively in the patients' quality of life. Some studies have evidenced the LLLT benefits in the gland function during the radiotherapy treatment. However, the results of the present pilot study show that in patients submitted to a 45 Gy minimum dosimetry in head and neck, 12 LLLT sessions applied for six weeks, were unable to promote salivary flow increase. The degree of cell destruction due to teletherapy, especially on the parotids, might have been one of the main factors associated with the results obtained. Nevertheless, xerostomia and quality of life showed improvement, thus highlighting the importance of advice and follow-up to the irradiated patients. New therapeutical modalities, especially in tissue engineering, must be further investigated in order to restore the gland function and, therefore, improve the quality of life of the patients with radiotherapy sequelae.

CONCLUSIONS

In the parameters used, LLLT was not able to increase SFR, or decrease xerostomia, hence the hypothesis that LLLT could stimulate residual gland function in patients treated with head and neck radiotherapy has not been confirmed. The results may be associated to the late effects of radiotherapy on glandular structure such as fibrosis and acinar atrophy.

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AUTHOR DISCLOSURE STATEMENT

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5 DISCUSSÃO GERAL

A saliva é de suma importância para a manutenção da homeostase oral e geral, desempenhando papel crucial nas funções digestiva e gustativa, limpeza e hidratação da mucosa bucal, proteção dos dentes e controle da microflora oral devido às suas propriedades antibacteriana, antifúngica e antiviral (AMERONGEN; VEERMAN, 2002; PORTER; SCULLY; HEGARTY, 2004; FARSI, 2007; THELIN, et al., 2008; FUJIMAKI, et al., 2014). Diversos fatores estão envolvidos nas disfunções salivares tais como fármacos (SREEBNY; SCHWARTZ, 1997; SCULLY, 2003; TURNER; JAHANGIRI; SHIP, 2008), alterações relacionadas ao envelhecimento (PERCIVAL; CHALLACOMBE; MARSH, 1994, TYLENDA; SHIP; FOX, 1988), doenças sistêmicas (GUGGENHEIMER; MOORE, 2003), radioterapia direcionada à região de cabeça e pescoço (EISBRUCH, et al., 2001; JENSEN, et al., 2010; KONINGS; COPPES; VISSINK, 2005), dentre outros.

Os mecanismos pelos quais a radiação ionizante causa danos às glândulas salivares permanecem pobremente compreendidos. Konings, Coppes e Vissink (2005) sugerem que a injúria esteja relacionada ao dano a membrana plasmática das células glandulares. Os radicais livres formados pela ação da radiação ionizante atuam sobre os canais lipídicos da membrana, alterando a ação dos receptores muscarínicos. Em uma fase tardia o dano à função glandular é marcado por redução na quantidade de células acinares funcionais, causado pela morte de células progenitoras e células-tronco (KONINGS; COPPES; VISSINK, 2005).

Apesar dos esforços na tentativa de estabelecer-se um protocolo de tratamento para a xerostomia e hipossalivação decorrentes da radioterapia, não há uma terapêutica-padrão. O presente estudo propôs o emprego da TLBP para o

manejo de disfunções salivares decorrentes da radioterapia. Este estudo diferencia-se dos demais que empregaram a TLBP em pacientes irradiados pela utilização dessa modalidade terapêutica em indivíduos que haviam finalizado a radioterapia há pelo menos seis meses. Foram selecionados 23 pacientes submetidos a regime radioterápico semelhante para tratamento de neoplasias malignas na região de cabeça e pescoço. Quanto à composição dos grupos, apesar da randomização, no grupo-controle houve predomínio de pacientes do sexo masculino, enquanto no grupo-laser o número de pacientes dos sexos masculino e feminino foi semelhante. Dois pacientes do grupo-laser sofreram excisão bilateral das glândulas submandibulares e seis foram submetidos à excisão unilateral desta glândula durante o tratamento cirúrgico da neoplasia maligna. No grupo-controle nenhum dos 11 pacientes sofreu excisão de ambas as submandibulares e oito indivíduos foram submetidos à excisão unilateral. Nos demais itens tais como idade, alterações sistêmicas e uso de medicamentos a distribuição dos grupos demonstrou homogeneidade.

Os efeitos da teleterapia sobre as glândulas salivares são observados desde o início do tratamento e os danos passam a ser irreversíveis após doses cumulativas de 26 a 39 Gy (VISSINK et al., 2010; PORTER; FEDELE; HABBAB, 2010). Dos 23 pacientes da amostra deste estudo, 15 receberam dose de radiação de 70 Gy, além de portais terapêuticos bilaterais (com irradiação de ambas as parótidas), acarretando níveis severos de hipossalivação, muitas vezes próximos à completa ausência de saliva (DE BARROS PONTES; POLIZELLO; SPADARO, 2004).

Conforme discutido no artigo de pesquisa, a hipótese de que a TLBP pudesse estimular a função glandular residual nos pacientes irradiados não foi confirmada no estudo. Não foi observada diferença significativa entre os grupos laser e controle

quanto à velocidade do fluxo salivar, em repouso e sob estimulação, ou quanto aos escores de xerostomia e qualidade de vida. Em estudos prévios, a TLBP foi aplicada concomitantemente à radioterapia (COWEN et al.,1997;LOPES; MAS; ZÂNGARO, 2006; SIMÕES et al., 2010; OTON-LEITE et al., 2013), promovendo redução da xerostomia e elevação do fluxo salivar. Na presente investigação, a TLBP foi empregada após o término da radioterapia, quando os pacientes já apresentavam importante disfunção salivar. Podem-se atribuir os resultados negativos da TLBP sobre o fluxo salivar às alterações morfológicas promovidas pela radiação ionizante na estrutura glandular tais como atrofia acinar e fibrose.

Entretanto, em ambos os grupos, houve redução da xerostomia e melhora da qualidade de vida relacionada à saúde oral. Durante o estudo todos os pacientes foram esclarecidos sobre hipossalivação e xerostomia, receberam instruções de higiene oral e foram orientados a manter a mucosa bucal hidratada e a evitar o uso de alimentos condimentados, de bebidas com teor ácido e de fumo ou álcool. O acompanhamento dos pacientes durante o estudo foi o fator preponderante à melhora das variáveis subjetivas xerostomia e qualidade de vida.

Para avaliação da xerostomia empregamos a EVA, um instrumento bem estabelecido na mensuração da dor (AITKEN, 1969; NGAN; KESS; WILSON, et al., 1989; LIM, et al., 1995). Pai et al. (2001) e Jham et al. (2007) sugeriram este como um método seguro, de fácil aplicação e importante na mensuração da xerostomia. A xerostomia, mesmo que variando em sua intensidade, é um sintoma que inevitavelmente interfere no bem-estar dos pacientes irradiados (GUCHELAAR; VERMES; MEERWALDT, 1997), portanto, optamos por avaliar também a qualidade de vida relacionada à saúde oral. Levando-se em consideração a redução nos escores do OHIP-14 ao longo das seis semanas de estudo, fica evidente a relação

entre a percepção de alivio da xerostomia e a melhora na qualidade de vida dos pesquisados.

A TLBP ainda carece de padronização em pesquisas, uma vez que muitos estudos não descrevem adequadamente todos os parâmetros metodológicos, além da grande variação em relação aos aparelhos utilizados. Deve-se considerar também que não há estudos prévios empregando a TLBP em tecido glandular já irradiado e apresentando as alterações morfológicas descritas previamente. Esses fatores dificultaram a determinação da metodologia deste estudo, principalmente quanto à energia a ser empregada por ponto, número e frequência de sessões de TLBP. Como o objetivo desta terapia é entregar uma quantidade específica de energia ao tecido-alvo, o parâmetro energia pode ser considerado o principal a ser determinado nos estudos (GARCEZ; RIBEIRO; NÚÑEZ, 2012). As propriedades ópticas de um tecido em situação patológica diferem daquelas de um tecido sadio (GARCEZ; RIBEIRO; NÚÑEZ, 2012). No presente estudo a TLBP foi aplicada em um tecido glandular que apresentava uma série de alterações decorrentes da radiação ionizante. Em função destas alterações como fibrose e redução da celularidade, que poderiam acarretar em menor distribuição da energia aplicada, optou-se por utilizar 2J de energia por ponto, valor superior ao dos demais estudos em que a TLBP foi utilizada concomitante à radioterapia. Para obtenção de 2 J de energia utilizando-se potência de 100 mW e um aparelho com spot de 0,03 cm^2, foi necessário aplicar-se dosimetria de 70 J/cm^2. Em pesquisas prévias em ratos e em humanos submetidos à radioterapia, foram aplicadas de quatro a trinta sessões de TLBP (LOPES, MAS, ZÂNGARO, 2006; SIMÕES, et al., 2008; SIMÕES, et al., 2010; LONCAR, et al., 2011). No presente estudo determinamos a frequência de duas sessões semanais, em vez de sessões diárias a fim garantir a adesão dos pacientes

da amostra à terapia, uma vez que muitos necessitavam deslocar-se de outras cidades da região. Por tratar-se de um estudo-piloto optamos por não estender demasiadamente o período experimental, estipulado em seis semanas, totalizando 12 sessões de TLBP.

A radioterapia realizada em região de cabeça e pescoço é uma das principais causas de disfunções salivares. Visando prevenir tais alterações, alguns estudos têm evidenciado os benefícios da TLBP na função glandular quando empregada de forma concomitante à radioterapia. Na presente investigação, realizada em pacientes submetidos à dosimetria mínima de 45 Gy de radiação ionizante, os resultados demonstraram que 12 sessões de TLBP aplicadas durante seis semanas não promoveram elevação do fluxo salivar. As alterações tardias promovidas pela teleterapia nas glândulas salivares maiores tais como atrofia acinar e fibrose foi provavelmente o fator que determinou os resultados deste estudo. Por outro lado, a melhora dos índices subjetivos xerostomia e qualidade de vida ressalta a importância da orientação e acompanhamento dos pacientes irradiados. Novas modalidades terapêuticas, principalmente na área de engenharia tecidual, devem ser investigadas para promover o restabelecimento da função glandular e consequente melhora na qualidade de vida nos pacientes portadores de sequelas decorrentes da radioterapia.

O efeito da TLBP utilizada de forma preventiva, ou seja, concomitante à radioterapia também deve ser investigado em outras pesquisas pré-clinicas e clínicas no intuito de determinar as alterações histológicas e moleculares promovidas no tecido glandular, além de estabelecer um protocolo-padrão de laserterapia a ser utilizado nesses pacientes.

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ANEXO A

APROVAÇÃO DA COMISSÃO CIENTÍFICA E DE ÉTICA DA FACULDALDE DE ODONTOLOGIA DA PUCRS

Comissão Científica e de Ética
Faculdade da Odontologia da PUCRS

Porto Alegre 31 de outubro de 2012

O Projeto de: Dissertação

Protocolado sob nº:	0052/12
Intitulado:	Efeito clínico da laserterapia na hipossalivação e xerostomia decorrentes da radioterapia em região de cabeça e pescoço.
Pesquisador Responsável:	Profa. Dra. Fernanda Gonçalves Salum
Pesquisadores Associados:	Jamil Saleh
Nível:	Dissertação / Mestrado

Foi ***aprovado*** pela Comissão Científica e de Ética da Faculdade de Odontologia da PUCRS em *31 de outubro de 2012.*

Este projeto deverá ser imediatamente encaminhado ao CEP/PUCRS.

Profa. Dra. Ana Maria Spohr
Coordenadora da Comissão Científica e de Ética da
Faculdade de Odontologia da PUCRS

Av. Ipiranga, 6681, Prédio 06 sala 210
Porto Alegre /RS – Brasil – Cx. Postal:1429
90619-900

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ANEXO B

APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA DA PUCRS

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITO CLÍNICO DA LASERTERAPIA NA HIPOSSALIVAÇÃO E XEROSTOMIA DECORRENTES DA RADIOTERAPIA EM REGIÃO DE CABEÇA E PESCOÇO

Pesquisador: Fernanda Gonçalves Salum

Área Temática:

Versão: 1

CAAE: 10513712.7.0000.5336

Instituição Proponente: Pontifícia Universidade Católica do Rio Grande do Sul - PUC/RS

DADOS DO PARECER

Número do Parecer: 154.280

Data da Relatoria: 23/11/2012

Apresentação do Projeto:

Projeto de mestrado vinculado a FO. Bem estruturado. Objetivos e metodologia bem explicitadas. Critérios de inclusão e exclusão bem definidos.Estudo clínico, prospectivo, randomizado, cego, placebo-controlado. No presente estudo é necessário que utilizar o placebo do laser, para que se verifique o real efeito da laserterapia sobre a hipossalivação e xerostomia.A laserterapia não é empregada como protocolo padrão ao tratamento da xerostomia e hipossalivação. Pode ser empregada de modo coadjuvante aos tratamentos convencionais ou de forma isolada. Caso, por meio desta pesquisa, haja confirmação da eficácia da laserterapia no tratamento da xerostomia e hipossalivação, os indivíduos que fizeram parte do grupo placebo serão chamados para nova avaliação e laserterapia.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar o efeito clínico da laserterapia sobre a xerostomia e hipossalivação de pacientes submetidos à radioterapia para tratamento de neoplasias de cabeça e pescoço.

Objetivo Secundário:

Avaliar em pacientes submetidos à radioterapia em região de cabeça e pescoço:-o efeito da LLLT na hipossalivação, por meio de avaliação da velocidade do fluxo salivar;-o efeito da LLLT na xerostomia, por meio de escala analógica visual;-se a laserterapia, utilizada para o tratamento da hipossalivação e xerostomia, exerce influência na qualidade de vida relacionada à saúde bucal.

Avaliação dos Riscos e Benefícios:

Riscos:

Não há riscos referentes ao uso do laser terapêutico de baixa potência desde que paciente e profissional utilizem proteção ocular, conforme descrito no projeto de pesquisa.

Benefícios:

Elevação do fluxo salivar, diminuição da sensação de boca seca e melhoria na qualidade de vida dos pacientes.

Comentários e Considerações sobre a Pesquisa:

Serão selecionados para participar deste estudo 60 pacientes de ambos os sexos, submetidos à radioterapia para tratamento de neoplasias malignas de orofaringe há pelo menos seis meses. Os pacientes serão distribuídos aleatoriamente em dois grupos: Grupo-laser: n=30 e Grupocontrole: n=30. O pacientes serão selecionados no Serviço de Radioterapia do Hospital São Lucas (SERP) da PUCRS. Neste Serviço o regime radioterápico é realizado com o aparelho Theratronix, modelo Phoenix, unidade de teleterapia rotacional por Cobalto 60 (fótons), com energia de 1,25 MeV. Durante a anamnese serão registrados em ficha individual os dados de identificação do paciente, história médica, uso de medicamentos, antecedentes amiliares e hábitos de tabagismo e etilismo .

Será realizado o exame físico loco-regional e intrabucal. A xerostomia será avaliada por meio de escala visual analógica (EVA), desenvolvida por Pai et al. (2001) e utilizada por Jham (2006) para avaliação deste sintoma. Esta escala consiste de oito itens relacionados à xerostomia e quantificados por meio de linhas horizontais medindo 10 cm de extensão. Os valores estão compreendidos entre o zero (que significa ausência do sintoma) e dez

(sintomatologia máxima). Os pacientes serão orientados a marcar um traço vertical sobre a linha relacionada a cada um dos itens. Para a mensuração do fluxo salivar, serão obtidas amostas de saliva total. Para coleta da saliva total em repouso, o paciente deverá evitar a movimentação, incluindo pequenos movimentos da língua, bochechas, mandíbula ou lábios. Os lábios devem ser mantidos ligeiramente abertos permitindo que a saliva escoe passivamente dentro de frasco de polipropileno graduado. O tempo de execução do processo deverá ser de 15 minutos. Para a coleta sob estimulação será empregado estímulo mecânico. Os pacientes serão orientados a mastigar um cilindro de látex medindo 1,0 cm de omprimento por 0,5 cm de diâmetro preso a um pedaço de fio dental para evitar deglutição. O paciente deverá mastigar a peça durante um minuto e depois remover toda a saliva por expectoração ou deglutição. A mastigação deverá prosseguir por um período de 5 minutos com o mesmo dispositivo de látex. A cada minuto o paciente deve expelir o conteúdo acumulado no frasco. A qualidade de vida dos pacientes será avaliada por meio do intrumento OHIP-14 (Oral Health Impact Profile), versão em português, traduzida e validada por Oliveira e Nadanovsky (2005). Os itens do OHIP-14 são agrupados em sete subscalas: limitação

funcional, dor física, desconforto psicológico, limitação física, limitação psicológica, limitação social e incapacidade. As aplicações do laser serão realizadas no ambulatório do Serviço de Estomatologia e Prevenção do Câncer Bucomaxilofacial do Hospital São Lucas-PUCRS. Os pacientes do grupo laser serão submetidos a duas aplicações semanais de radiação laser de diodo durante seis semanas, totalizando 12 sessões. As aplicações serão realizadas nas glândulas salivares maiores, de forma pontual e contínua. Serão aplicados
três pontos sobre cada glândula parótida, dois pontos sobre cada submandibular e dois pontos sobre cada sublingual na dosimetria de 199 J/cm² totalizando energia de 6 J por ponto. No grupo controle os procedimentos serão os mesmos, no entanto com o aparelho desligado, onde um timer emitirá um sinal sonoro mimetizando a aplicação do grupo laser. A escala visual analógica, o instrumento OHIP-14 e a coleta de saliva serão realizadas nos momentos baseline, sexta sessão e décima segunda sessão.

Considerações sobre os Termos de apresentação obrigatória:

- TCLE , ok;
- folha de rosto, ok;
- Autorização para uso das dependências do serviço de estomatologia e prevenção do câncer bucomaxilofacial, ok;
- Carta da CCFO, ok;
- Termo de confidencialidade para uso de dados, ok;
- Autorização para acessar dados dos prontuários de radioterapia, ok;
- Lattes, ok;
- Orçamento, ok.

Recomendações:

Não há recomendações a fazer.

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências e inadequações no presente protocolo.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Parecer de acordo com a reunião do colegiado.

PORTO ALEGRE, 26 de Novembro de 2012

Assinador por:
Rodolfo Herberto Schneider
(Coordenador)

ANEXO C

Escala visual analógica

1. Marque a dificuldade que você tem para falar devido à secura

Não é difícil 0----------10 Muito difícil

2. Marque a dificuldade que você tem para engolir devido à secura

Não é difícil 0----------10 Muito difícil

3. Marque a quantidade de saliva na sua boca

Muita saliva 0----------10 Nenhuma saliva

4. Marque a secura da sua boca

Não é seca 0----------10 Muito seca

5. Marque a secura da sua garganta

Não é seca 0----------10 Muito seca

6. Marque a secura dos seus lábios

Não são secos 0----------10 Muito secos

7. Marque a secura da sua língua

Não é seca 0 ----------10 Muito seca

8. Marque o grau da sua sede

Não sinto sede 0----------10 Sinto muita sede

ANEXO D

OHIP-14 (ORAL HEALTH IMPACT PROFILE)

REPRODUÇÃO DO "PERFIL DE IMPACTO NA SAÚDE ORAL" (OHIP14)[36]

Nos últimos seis meses, por causa de problemas com seus dentes ou sua boca:	Nunca	Raramente	Às vezes	Repetidamente	Sempre
1. Você teve problemas para falar alguma palavra?					
2. Você sentiu que o sabor dos alimentos tem piorado?					
3. Você sentiu dores em sua boca ou nos seus dentes?					
4. Você se sentiu incomodado(a) ao comer algum alimento?					
5. Você ficou preocupado(a)?					
6. Você se sentiu estressado(a)?					
7. Sua alimentação ficou prejudicada?					
8. Você teve que parar suas refeições?					
9. Você encontrou dificuldade para relaxar?					
10. Você se sentiu envergonhado(a)?					
11. Você ficou irritado(a) com outras pessoas?					
12. Você teve dificuldade para realizar suas atividades diárias?					
13. Você sentiu que a vida, em geral, ficou pior?					
14. Você ficou totalmente incapaz de fazer suas atividades diárias?					

ANEXO E

SUMISSÃO DO ARTIGO DE REVISÃO DA LITERATURA NO PERIÓDICO

ARCHIVES OF ORAL BIOLOGY

Submission Confirmation for SALIVARY HYPOFUNCTION: AN UPDATE ON ETIOLOGY, DIAGNOSIS AND THERAPEUTICS

ees.aob.0.27aea2.5d179d91@eesmail.elsevier.com em nome de Archives of Oral Biology [AOB@elsevier.com]

Enviado: quarta-feira, 5 de março de 2014 10:14
Para: Fernanda Goncalves Salum; fernanda_salum@hotmail.com

Archives of Oral Biology
Title: SALIVARY HYPOFUNCTION: AN UPDATE ON ETIOLOGY, DIAGNOSIS AND THERAPEUTICS
Authors: jamil saleh; Maria A Figueiredo, PhD; Karen Cherubini, PhD; Fernanda G Salum, PhD
Article Type: Review Article

Dear Fernanda,

Your submission entitled "SALIVARY HYPOFUNCTION: AN UPDATE ON ETIOLOGY, DIAGNOSIS AND THERAPEUTICS" has been received by Archives of Oral Biology.

You may check on the progress of your paper by logging on to the Elsevier Editorial System as an author. The URL is http://ees.elsevier.com/aob/.

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Thank you for submitting your work to this journal. Please do not hesitate to contact me if you have any queries.

Kind regards,

(On behalf of the Editors)

Archives of Oral Biology

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ANEXO F

SUMISSÃO DO ARTIGO DE PESQUISA NO PERIÓDICO

PHOTOMEDICINE AND LASER SURGERY

Photomedicine and Laser Surgery - Manuscript ID PHO-2014-3741
onbehalfof+photomedicine.editorial+gmail.com@manuscriptcentral.com em nome de photomedicine.editorial@gmail.com
Enviado: segunda-feira, 17 de março de 2014 14:18
Para: Fernanda Goncalves Salum

17-Mar-2014

Dear Dr. Salum:

Your manuscript entitled "EFFECT OF LOW-LEVEL LASER THERAPY ON RADIOTHERAPY-INDUCED HYPOSALIVATION AND XEROSTOMIA: A PILOT STUDY" has been successfully submitted online and is presently being given full consideration for publication in Photomedicine and Laser Surgery.

However, we would like to inform you that if your manuscript, which includes text, abstract, references and tables or figures, is not formatted according to the author instructions, we will not be able to process your submission. We will notify you of the changes to be made and unsubmit your paper, enabling you to implement the formatting corrections and re-submit once they are complete.

To help defray the publication costs as we increase the number of articles we publish in each issue, for manuscripts submitted after January 1, 2010 the Journal is implementing page charges of $60 per printed page. Please note that payment of page charges can be waived under certain circumstances and is not a prerequisite for publication.

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