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Case Report

Topical and Systemic Photobiomodulator Treatment of Lingual Paresthesia Caused by Prolonged Use of Tamoxifen in a Patient with Breast Cancer

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Abstract

This study deals with the case of a patient in remission of breast cancer and paresthesia of the left lingual region promoted by prolonged use of the hormone Tamoxifen (TAM). The successful management to improve paresthesia was performed by Topical Photobiomodulation (PBMT) in the oral region and transdermal Systemic Photobiomodulation (PBMS) in the primitive carotid artery to reduce this lingual comorbidity, through the applications of the Low Level Laser Therapy (LLLT) equipment. This lingual dysfunction was resolved in 3 sessions, with excellent results and no side effects. The technique was performed by the dentist in a hospital environment and monitored by the multidisciplinary team.

Keywords: *Laser; Photobiomodulation; Lingual Paresthesia; Tamoxifen; Low Level Laser Therapy*

Introduction

The World Health Organization (WHO) estimates that around 1.38 million new cases of breast cancer and 458 thousand deaths due to the disease of new cases occur worldwide, with this tumor being more prevalent among women and also represents the leading cause of cancer death among Brazilian women [1].

According to data from the Brazilian Society of Mastology, about one in 12 women will have a breast tumor by the age of 90. In Brazil, according to the National Cancer Institute (INCA), almost 60 thousand new cases were diagnosed, which represents an incidence rate of 51.29 cases per 100 thousand women [2,3].

In breast cancers that evolve to Invasive Ductal Carcinoma, about 65 to 85% are related to hormone receptors on the cell surface [3]. This cancer can grow locally and reach other sites, through veins and/or lymphatic vessels through a process of metastasis.

These hormone receptors play an extremely important role in the adjuvant hormonal treatment of patients with invasive cancer, which are considered to be a beneficial factor, since one of the most widely used drugs for the treatment of breast cancer, TAM, has a direct antagonistic action on the receptors of estrogen of tumor cells causing a reduction in the transcription of genes regulated by this receptor, which leads to a decrease in the growth of cancer cells in the breast [4]. TAM was used to treat breast cancer cells and is considered the first drug to be used in hormone therapy and to be used as chemopreventive, having been used since the 1970s in hormonal therapies for malignant breast carcinoma. In addition to the treatment of breast cancer, TAM is also used as a protective agent against coronary diseases, thanks to its ability to prevent the formation of atheromatous plaques [3-5].

The side effects of TAM are, in general, moderate, among which include several adverse effects (Table 1) such as nonspecific paresthesias that are manifested due to cytotoxicity in the Central Nervous System (CNS) affecting in certain cases the lingual sensitivity in treatments for a long period with sensory changes in the Lingual Nerve [6].

Frequency	Systems	Adverse reactions
Very Common (≥ 10%)	Gastrointestinal changes	Nausea
	Changes in metabolism and nutrition	Liquid retention
	Changes in the reproductive system and breasts	Vaginal bleeding and vaginal discharge
	Changes in skin and subcutaneous tissues	Skin eruption
	Vascular changes	Fogachos
	General changes and status of the administration	Fatigue
Common (≥ 1 - < 10%)	Changes in the blood and lymphatic system	Anemia
	Changes of vision	Cataract and retinopathy
	Changes in the immune system	Hypersensitivity reactions
	Research	Elevation of triglyceride levels
	Musculoskeletal and connective tissue changes	Cramps and myalgia
	Benign, malignant and unspecified neoplasms	Uterine myomas
	Changes to the nervous system	Ischemic cerebrovascular events, headache,
	Changes in the reproductive system and breasts	Vulvar itching, endometrial changes (including
	Changes in skin and subcutaneous tissues	Alopecia
	Gastrointestinal changes	Vomiting, diarrhoea and constipation
	Hepatobiliary changes	Changes in liver enzymes and steatosis
	Multiple terms COS (class of organs and systems)	Thromboembolic events (including deep vein
Incommon (≥ 0,1 - < 1%)	Changes in the blood and lymphatic system	Thrombocytopenia and leukopenia
	Changes of vision	Visual changes
	Gastrointestinal changes	Pancreatitis
	Changes in metabolism and nutrition	Hypercalemia in patients with bone
	Benign, malignant and unspecified neoplasms	Endometrial cancer
	Respiratory, thoracic and mediastinal changes	Interstitial pneumonitis
	Hepatobiliary changes	Cirrhosis of the liver
Rare (≥ 0,01 - < 0,1%)	Changes in the blood and lymphatic system	Neutropenia and agranulocytosis
	Changes of vision	Corneal changes and optic neuropathy
	Benign, malignant and unspecified neoplasms	Uterine sarcoma (mainly Müller's mixed
	Changes in the reproductive system and breasts	Endometriosis, cystic ovarian oedema, vaginal
	Changes to the nervous system	optic neuritis
	Hepatobiliary changes	Hepatitis, cholestasis, liver failure,
	Changes in skin and subcutaneous tissues	Angioedema, Steven Johnson syndrome
Very rare (< 0.01%)	Changes in skin and subcutaneous tissues	Cutaneous lupus erythematosus
	Congenital, familial and genetic changes	Porphyria cutaneous tarda
	Procedure complications, injury and intoxication	Re-exacerbation of the dermatological condition

***Table 1:** Side effects of tamoxifen.*

Lingual sensitivity and motility is determined by the Lingual Nerve (NL). NL promotes the innervation of the anterior two thirds of the tongue. It is initially located in the external, medial pterygoid and in front of the lower alveolar nerve and is occasionally associated with this nerve by a branch that can cross the internal maxillary artery. The nerve travels between the internal pterygoid and the mandibular branch (Figure 1). Obliquely to the side of the tongue over the constrictor of the upper pharynx and styloglossus and then between the hyoglossus and the deep part of the submandibular gland; finally it crosses the duct of the submandibular gland and goes to the most anterior border of the tongue. Its branches innervate the sublingual gland, the mucous membrane of the mouth, the tonsils, the gums and the mucous membrane of the anterior two thirds of the tongue; the terminal filaments communicate at the tip of the tongue with the hypoglossal nerve [7,8].

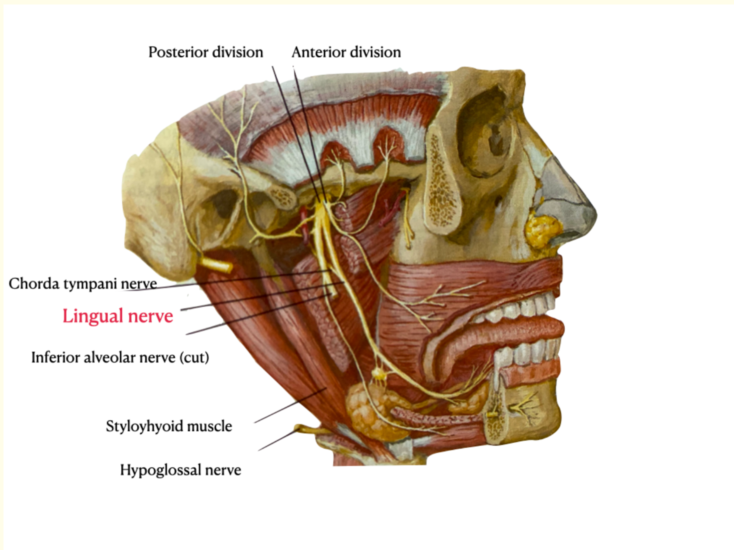

Figure 1: *Anatomical location of the Lingual Nerve (NL).*

This functional change in the tongue promoted by the TAM hormone blocker near the CNS has the possibility of causing a transient paresthesia with a negative impact on the oropharyngeal region.

Drug treatments with drugs (corticosteroids) or vitamins (Complex B) are considered the choice for the recovery of normal functions of patients suffering from paresthesia in several areas of the human body [9,10], however, in this study, a technological tool for precision, non-invasive and low cost: Low Level Laser Therapy (LLLT) that produces Photobiomodulation (PBM) effects.

The LLLT was initially researched to stimulate wound healing, reduce pain and inflammation in various changes, such as tendonitis, cervical pain and carpal tunnel syndrome [11]. The advent of light-emitting diodes led LLLT to be renamed "low level Laser Therapy", which subsequently determined PBM terminology.

The mechanism of action of PBM revolves around Cytochrome C Oxidase (CCO), which is one of the units of the mitochondrial respiratory chain, responsible for the final reduction of oxygen in water, using the electrons generated by glucose metabolism [12]. The activity of the CCO enzyme can be inhibited by nitric oxide (NO). The repressed NO can be dissociated by photons of light that are absorbed by the CCO (Figure 2). These absorptions are carried out by the red wave (600 - 700 nm) and near infrared (760 - 940 nm). The more NO is dissociated, the more oxygen will be consumed [13].

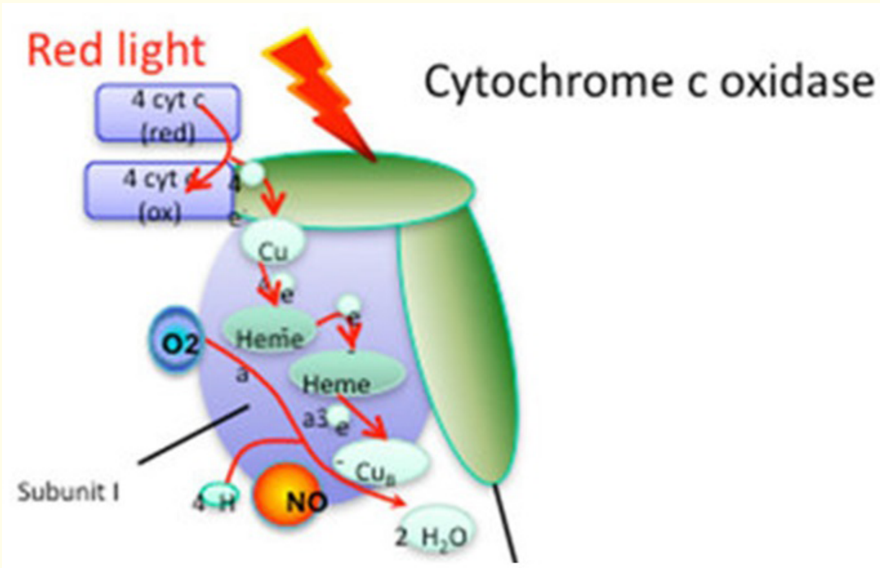

Figure 2: *Biochemical mechanism of COC under red light.*

The increase in reactive oxygen species (ROS) produced in mitochondria absorbs photons delivered during PBM to trigger some mitochondrial signaling pathways leading to cytoprotective, anti-oxidant and anti-apoptotic effects in cells [14]. There will be a vasodilator process with increased blood flow, which provides an efficacy regarding the use of Laser therapy on the affected site, mainly as an indication of treatment for long-term sensory disorders [15]. The LLLT becomes capable of reacting with photosensitive proteins, recovering the affected nervous tissue with a significant improvement in the dysfunctions of the compromised organ.

Case Report

Female patient, 60 years old, ED, diagnosed with invasive left breast carcinoma in 2012, underwent tumorectomy and axillary emptying in the same year, followed by chemotherapy (CT) - 2 CMF cycles (cyclophosphamide, methotrexate and 5-fluoracil), Radiotherapy, Tamoxifen for 5 years, Calcium and Vit D.

In April 2018, the patient presented to the Dentistry Service of the Ribeirão Preto Cancer Hospital with a complaint related to the left lingual region with symptoms that corresponded to motor and taste insensitivity with a diagnosis suggestive of lingual paresthesia (Figure 3). The patient added in the anamnesis that this symptom had been present for approximately 5 years and drug treatments and that she had already undergone several treatments that she was unable to specify.

Figure 3: *Lingual region in the initial phase.*

At the initial consultation, the entire oral cavity (hard and soft tissues) that were in normal condition was evaluated, except for the left lingual half that was insensitive (lingual paraesthesia) and resilient dysgeusia related to salt/sweet flavors (Figure 3). Additional markers complemented the chart: Blood Pressure 130 x 80 mm/Hg, capillary blood glucose 82 mg/dl, SPO_2 98% (O_2 saturation).

The proposed therapy for the treatment of paresthesia was PBMT and transdermal PBMS through LLLT (Therapy - DMC equipment - São Carlos - Brazil), power 100 mW for each Laser emitter, with dual wavelengths red (660 nm) and infrared (810 nm), tip area 0,098 cm^2 [16-18].

Irradiation parameters

The irradiation parameters of LLLT are measured through wavelength (nm), energy (joules), fluence (J/cm^2) (Table 2). Laser therapists and researchers have been based on the definition of the Laser dose by energy density, however the variety of Laser equipment available on the market today can alter the proposed therapeutic responses, due to changes in parameters that vary according to the manufacturer.

Irradiation Parameters	Unit of measurement	Description
Wavelength	nm	It is the laser emission characteristic defined by different colours of the visible (400 to 700 nm) and invisible spectrum
Fluence	J/cm^2	Fluency or dose is a description of the energy flow divided by the area of the laser emitter tip
Energy	Joule	Energy is represented by the power of the equipment multiplied by the treatment time

Table 2: *Description of irradiation parameters.*

Previous clinical conduct

Asepsis of the entire oral cavity with 0.12% chlorhexidine Digluconate mouthwash by digital friction through sterile gauze before each consultation and use of protective plastic on the active tip of the Laser device.

PBMT

Simultaneous application of the dual Laser (red and infrared) have been realigned into 3 specific treatment areas with the following parameters for each area:

- Total back extension of the tongue - with energy of 3 joules for each emitter per point, with points distancing 1.5 cm performing a total of 9 points (total time treatment 270 seconds) (Figure 4-6);
- Larger salivary glands in the sublingual, parotid and submandibular on the left - with energy of 2 joules for each emitter per gland over the anatomical regions of the glands - 1 point per gland in total 3 points (total time treatment 60 seconds) (Figure 7);
- Bottom region of vestibule of the left vestibular area, wavelength - with energy of 2 joules for each emitter per point (total time treatment 20 seconds) (Figure 8).

Figure 4: *Positioning of the active LASER tip on the lateral edge of the left tongue.*

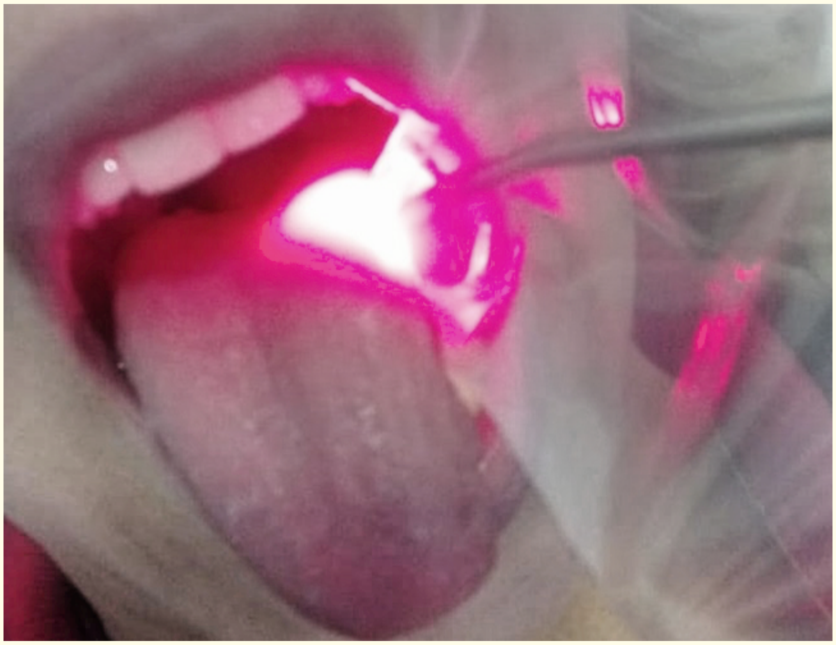

Figure 5: *LASER application over the entire left lateral border.*

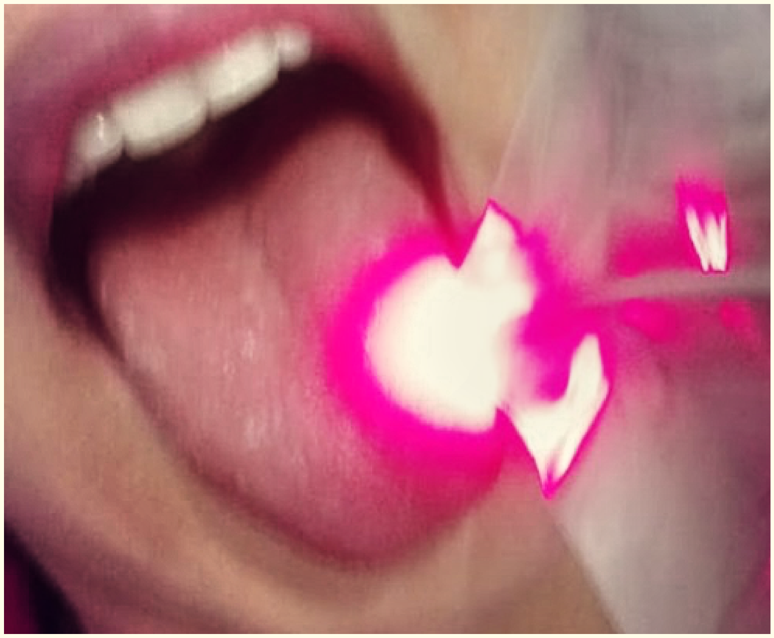

Figure 6: *LASER application over the entire left anterior border.*

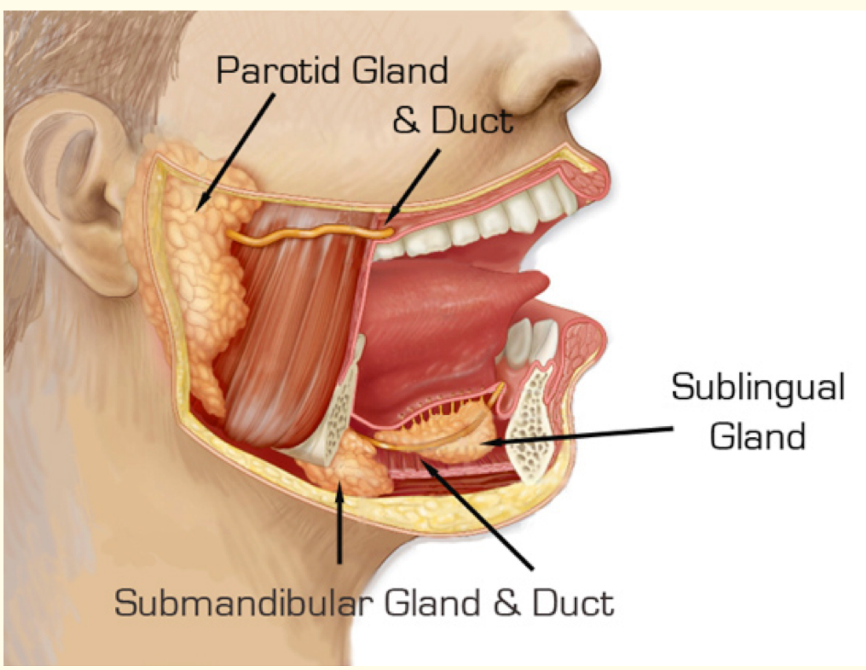

Figure 7: *Anatomical location of the major salivary glands.*

Figure 8: *Application of the LASER in the lobby.*

PBMS transdermic

The treatment was performed in the primitive carotid artery with the aid of a necklace adapted to the Therapy equipment Laser, in which a 15-minute application of uninterrupted red (660 nm) wavelength was performed. The total energy of the PBMS treatment was 90 Joules (Figure 9).

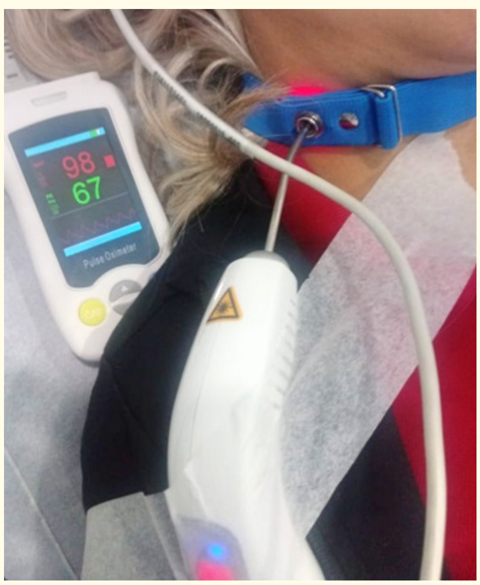

Figure 9: *Positioning and application of the active LASER tip on the right cervical collar in the anatomical region of the primitive carotid artery.*

Treatment time

A total of 3 appointments were carried out on a monthly basis, with the joint use of PBMT in the oral cavity and transdermal PBMS, until the complete remission of the left lingual paresthesia (Table 3 and 4).

Date of Appointment	Motor function	Sensitive function	Taste
02/04/2018	+	++	+
10/05/2018	+++	+++	+++
07/06/2018	++++	++++	++++

Table 3: *Functional language scale.*

Function	+	++	+++	++++
Motor	Very low motility	Low motility	Good motility	Reactive Normo
Sensitive	Absence of pain	Pressure and low pain	Moderate pain	Reactive Normo
Taste	Low	Moderate	Regular	Reactive Normo

Table 4: *Codification of the subjective analysis of tongue functions.*

Discussion

Paresthesia is a localized condition of numbness of the region innervated by the nerve in question where the main symptom is the lack of sensitivity in the affected region, but, in more advanced stages of paresthesia, the patient may report altered sensitivity to cold, heat and pain, numbness and tingling sensation. Paresthesia of the lingual nerve can also cause a burning sensation in the tongue, changes in taste, constant nibbling on the tongue and dysgeusia [19]. It can cause accumulation of food debris over the region of the jugal mucosa, frequent bites on the lip and/or tongue and burning of the lips with hot liquids.

In this case study, this paresthesia was associated with the drug use of TAM causing the neural cytotoxic effects that affected the sensory and motor functions of the tongue in the left portion.

The application of LLLT was presented as a proposal to help repair NL after drug cytotoxicity due to long-term hormone therapy, although this therapy is not acceptable as a definitive treatment protocol in all cases.

The findings of the present investigation demonstrated a significant recovery of mechano-receptor sensitivity among patients undergoing Laser therapy. It is important to report that there was no dysesthesia during the application of the Laser and that the tissue that presented with dysfunction improved after all applications with good evolution in the periodic intervals. The design of this study was to evaluate nerve function in an objective and subjective way through the ultra late effects of TAM.

The uses of LLLT for the recovery of lingual paresthesia are available with a wealth of global articles when the subject refers to the use of LLLT in the face of injury or compression of the lower alveolar nerve due to extraction of the lower third molars included, however, in this case study, the analogous use of Laser was partially reproduced, since it is similar symptoms, thus there was a surprising evolution with total recovery of the condition [20,21].

Transdermal PBMS used in an associative manner through the primitive carotid artery exerted an important activity in the systemic context, as it stimulated the activity of the CCO in normal healthy cells with the resulting increase in the potential of the mitochondrial membrane (MMP) above the normal baseline levels that led to normal an increase in the generation of reactive oxygen species (ROSs) by activating the redox-sensitive transcription factor, NF-kB. The addition of antioxidant N-acetyl-cysteine to cells can block NK-kB activation. In cultured cortical neuronal cells [22], the PBMS produced a high ATP response and, consequently, a greater nervous impulse among neural cells.

Conclusion

Over the years, LLLT has been punctually repairing neural injuries, especially in clinical cases related to compression or traction of the lower alveolar nerve with repercussions in the NL, due to mandibular surgery of greater invasiveness. The application of PBMT in association with PBMS did not increase the sensorineural response with physiological recovery in a few months from the paraesthesia that lasted over 5 years.

It is concluded that in some clinical cases LLLT has become effective in the treatment of lingual paresthesia, however, long-term randomized clinical studies are necessary to confirm the employability of this promising non-invasive treatment modality.

The evaluation of the results obtained with the PBMT/PBMS for the treatment of orofacial paresthesia is still mainly in the subjective field, which can represent an important evaluation trend, since the individual responses of human beings can vary considerably. More objective methods should be investigated to ensure greater reliability in cases of follow-up similar to that presented in this article.

The technique of using the two Laser wavelengths together in the 3 sessions seems to have some role in the result, possibly due to the constant stimulation of different chromophores throughout the course of treatment.

It is of utmost importance that the evolution of researches similarly invest in the creation of new repairing protocols with the use of low intensity Laser to minimize the cytotoxic effects of the oropharyngeal region caused by the use of oncological hormonal drugs.

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Conflicts of Interest

The authors have no conflict of interest to declare.

Bibliography

1. World Health Organization. “WHO report on cancer: setting priorities, investing wisely and providing care for all”. World Health Organization (2020).

2. Instituto Nacional de Câncer José Alencar Gomes da Silva. “A situação do câncer de mama no Brasil: síntese de dados dos sistemas de informação”. Instituto Nacional de Câncer José Alencar Gomes da Silva”. – Rio de Janeiro: INCA (2019).

3. Nascimento., *et al.* “Análise dos principais métodos de diagnóstico de câncer de mama como propulsores no processo inovativo”. *Arquivos de Medicina* 29.6 (2015): 153-159.

4. Bernardes JR., *et al.* “Estudo da atividade hormonal de mulheres tratadas com tamoxifeno no menacme”. *Revista Brasileira de Ginecologia e Obstetrícia* 20.9 (1998): 533-536.

5. Fernandes Luzia., *et al.* “Efeito do Tamoxifeno no metabolismo lipídico de pacientes portadoras de câncer de mama”. *Revista Eletrônica de Farmácia* 2 (2008): 61-63.

6. Denk Franziska., *et al.* "Tamoxifen induces cellular stress in the nervous system by inhibiting cholesterol synthesis". *Acta Neuropathologica Communications* 74.26 (2015).

7. Fagan SE., *et al.* "Anatomy, Head and Neck, Lingual Nerve". In: StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing (2020).

8. Stéphane J Montuelle., *et al.* "Unilateral lingual nerve transection alters jaw-tongue coordination during mastication in pigs". *Journal of Applied Physiology* (2020).

9. Benevides Ramon., *et al.* "Parestesia do nervo alveolar inferior após exodontia de terceiros molares inferiores: da prevenção ao tratamento". *Full Dentistry in Science* 9 (2018): 66-71.

10. Moon S., *et al.* "Hypoesthesia after IAN block anesthesia with lidocaine: management of mild to moderate nerve injury". *Restorative Dentistry and Endodontics* 37.4 (2012): 232-235.

11. Toshihiro Kushibiki and Miya Ishihara. "Biological Function of Low Reactive Level Laser Therapy (LLLT)" (2017).

12. Hamblin Michael. "Mechanisms and applications of the anti-inflammatory effects of photobiomodulation". *AIMS Biophysics* 4 (2017): 337-361.

13. Negri LB., *et al.* "Photobiomodulation combined with photodynamic therapy using ruthenium phthalocyanine complexes in A375 melanoma cells: Effects of nitric oxide generation and ATP production". *The Journal of Photochemistry and Photobiology B* 198 (2019): 111564.

14. Hamblin MR. "Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation". *Photochemistry and Photobiology* 94.2 (2018): 199-212.

15. Oishi JC., *et al.* "Hypotensive acute effect of photobiomodulation therapy on hypertensive rats". *Life Sciences* 178 (2017): 56-60.

16. Juliano Abreu Pacheco. "Applied Transdérmic Photobiomodulator Therapy About the Primary Carotide Artery in Patients Under Hormonal Blockers and Dynude Disorders and Pathogenic Flora of Orofaringeo and Systemic Repercussions". *American Journal of Biomedical Science and Research* 4.4 (2019).

17. Pacheco JA., *et al.* "Successful Management of Dysgeusia by Photobiomodulation (PBM) in a Cancer Patient". *Journal of Medical Case Reports* 2 (2019): 114.

18. Lacerda-Santos., *et al.* "Fototerapia no tratamento da mucosite oral: uma revisão de literature". (2019).

19. Migiyama Larissa Iane do Carmo Estudo da parestesia dos nervos alveolar inferior e lingual/Larissa Iane do Carmo Migiyama, Luma Quirino Souza, Universidade de Taubaté, Departamento de Odontologia (2019).

20. Merigo E., *et al.* "At-home laser treatment of oral neuronal disorders: Case reports". *Journal of Clinical and Experimental Dentistry* 9.4 (2017): e595-e598.

21. Ozen Tuncer., *et al.* "Efficacy of Low level laser therapy on neurosensory recovery after injury to the inferior alveolar nerve". *Head and Face Medicine* 2 (2006): 3.

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