**Case report**

**Effect of Vascular Photobiomodulation in a patient with severe xerostomia: Clinical case report**

**ABSTRACT**

Fluoxetine is a widespread antidepressant medication, with side effects, including xerostomia. In search of treatments to reduce discomfort, PBM is one of the alternatives that has proven to be effective. This article aims to demonstrate the clinical evolution of a female patient, L.R.O., 55 years old, who reported severe oral discomfort due to lack of saliva. The selected treatment was the Low Power Laser - EccoFibras with vascular photobiomodulation, in radial artery for 30 minutes, wavelength 660nm and power of 100mW, with 180J energy delivery. After the first treatment session, the patient reported improvement and satisfaction and, due to the unpredictability of psychiatric discharge, she tried to perform weekly applications. With each session, she reported a decrease in symptoms, which encouraged her attendance. With the prevention of xerostomia, the pacient achieved a clear increase in her quality of life, demonstrating that vascular photobiomodulation can be an interesting low-cost non-invasive treatment.

KEYWORDS: xerostomia, photobiomodulation, laser therapy, side effects.

**INTRODUCTION**

Total saliva is a complex of secretions that come in part from the pairs of parotid, submandibular and sublingual glands, and in part from numerous minor salivary glands distributed in the oral mucosa (Mese, 2007). In the mouth, this compound is formed by gingival fluid, desquamated epithelial cells, microorganisms, products of bacterial metabolism, food residues, leukocytes, mucus from the nasal cavity and pharynx. Saliva has several functions, including tissue repair, buffering, protection, digestion, taste, antimicrobial action, maintenance of tooth integrity and antioxidant defense system. (Falcão, 2013).

Saliva, as the first digestive fluid in the alimentary canal, assists in the ingestion of food and the digestion of starch and lipids, acting as a solvent. Saliva also plays a crucial role in hydrating and maintaining the taste receptor and oral mucosa and protecting the teeth. Furthermore, saliva controls oral microflora with its antimicrobial properties and mechanical cleaning action. Therefore, the loss of salivary function can have several serious consequences (Abueva, 2022).

The “unstimulated” flow is approximately 0.3 to 0.4mL/min but with wide variation between subjects and is sustained presumably by minor reflex activity and central nervous system activity since the flow of saliva decreases during sleep to around 0.1mL/min (Proctor, 2021). However, the speed at which saliva reaches the mouth shows great variation between individuals (Proctor, 2016). Parasympathetic stimulation results in increased saliva secretion through cholinergic transmission and action on M3 muscarinic receptors, while sympathetic stimulation alters salivary protein content through noradrenergic transmission and action on α and β receptors (de Almeida, 2008).

Several factors are capable of altering salivary flow. Such changes may vary from individual to individual, and in the same individual under different circumstances. Body hydration, tobacco use, medication use, saliva stimulation, some illnesses, among other factors, are capable of generating changes in salivary production. (Almeida, 2008). Complaints of dry mouth occur when there is insufficient production of saliva or changes in its composition. Dry mouth is called xerostomia, and one of the most common causes is due to the side effect of medications (Scully, 2003).

Drug-induced hyposalivation also can be an extension of the drug’s intended action, as seen with the parasympatholytic agents (such as atropine), or as an anticholinergic side effect withdrugs such as tricyclic antidepressant (Guggenheimer, 2008). Hyposalivation is a condition that can be very debilitating for patients and is likely to be increasingly common, so dentists should be aware of its diagnosis and treatment. (Mese, 2007)

 Medications with anticholinergic activity can cause hyposalivation by decreasing acetylcholine released by the parasympathetic system (Turner, 2016). Both the parasympathetic and sympathetic nervous systems innervate the salivary glands (Guggenheimer, 2008). SNRIs are believed to produce central accumulation of norepinephrine, activation of α2 receptors, and inhibition of parasympathetic salivary neurons in the brainstem, resulting in decreased salivary secretion. (Proctor, 2016).

Salivary dysfunction may be accompanied by symptoms of dry mouth, called xerostomia. The presence of xerostomia is not predictive of hyposalivation, as both conditions can manifest independently. However, the greater the hyposalivation, the greater the patient's tendency to present xerostomia (Pedersen, 2018). Reduced salivary flow is a common disorder, and it is estimated that around 20% of the general population has this change. (Falcão, 2013).

According to the World Health Organization (2017), mental disorders are common and contribute to morbidity, disability, injuries and premature mortality and increasing the risk and involvement of other health conditions. Worldwide, it is estimated that more than 300 million people, of all ages, suffer from depression, equivalent to 4.4% of the world population, being more prevalent among women.

Psychiatric medications can cause side effects with repercussions on the stomatognathic system, such as hyposalivation (Kossioni, 2013). Patients who use medication for a long time experience side effects with repercussions on the oral cavity, for example, on the salivary glands, altering the flow and composition of saliva (de Ameida, 2012). It is worth mentioning that side effects represent one of the main reasons for discontinuing treatments (Bull, 2002).

A study analyzed medications and observed ten out of 15 antidepressants showed significantly higher rates of short-term dry mouth than placebo, with the following decreasing order of incidence: duloxetine, desvenlafaxine, reboxetine, venlafaxine, sertraline, bupropion, paroxetine, escitalopram, levomilnacipran and fluvoxamine. Five out of 15 antidepressants (agomelatine, citalopram, fluoxetine, mirtazapine and vortioxetine) did not differ from placebo in terms of dry mouth rates (Oliva, 2021). In another bibliographic survey it was reported fifty-six medications showed strong evidence of interference with the function of the salivary glands, thirty-six of which belonged to the main nervous system category of the ATC (Anatomical Therapeutic Chemical), and the most cited in the literature are oxybutynin (21 articles), tolterodine (19 ), duloxetine (19), quetiapine (14), bupropion (12), olanzapine (11), solifenacin (11), clozapine (9), fluoxetine (9) and venlafaxine (8) (Wolff, 2017).

Fluoxetine is an effective antidepressant when administered in dosages of 20 to 80 mg per day (60 to 80 mg being clinically usual) for patients with unipolar depression (Benfield, 1986). The approved dose range is up to 80 mg/day, and when higher doses are used, adverse events are more common (Wernicke, 2004). Adverse events commonly associated with the initiation of fluoxetine therapy tended to decrease, and no adverse events reported initially became more frequent at the end of therapy (Zajecka, 1999). Dysgeusia has been reported following administration of fluoxetine (Wolff, 2017).

Clinical signs of dry mouth, identified during a physical examination, include glossy oral mucosa, altered gingiva, fissured tongue or loss of lingual papillae, and foamy saliva. Once a diagnosis is made and an underlying etiology is identified, there are many therapeutic options for management that can help alleviate the clinical manifestations of xerostomia (Millsop, 2017).

The theory of stimulated emission was first described by Einstein in 1917. The word LASER is the acronym for “Light Amplification by Stimulated Emission of Radiation” (Genovese, 2007).

The mechanisms involved in the treatment of PBM are not yet completely understood. However, the main idea is that photons are absorbed by the target tissue, converting them into useful energy that enhances metabolic processes in the cell, such as increased ATP production and the production of reactive oxygen species (ROS) (Sousa, 2019).

Low-power laser light therapy has been shown to be effective in the treatment of the most diverse conditions or diseases, as it promotes biomodulation of cellular metabolism, analgesia and anti-inflammatory effects, without mutagenic and photothermal effects (Gonelli, 2016). Its effects are based on transforming laser light into biomodulatory energy (Saleh, 2014).

The photobiomodulation effect depends on the number of absorbed photons which is correlated to the wavelength, the photon delivery rate (power) and the correct selection of spectrum and time parameters (Schubert, 2007). There is some research on the use of photobiomodulation to recover salivary glands and increase salivary flow. However, there is great variability between studies according to the photobiomodulation light parameters used and therefore results are rarely comparable (Golez, 2022). The wavelength used in low-level laser therapy is not fixed, so it is worth studying the laser equipment and defining the wavelength indicated for therapeutic efficacy. (Xu, 2015).

Photobiomodulation, previously called low-intensity light therapy (LLLT), is a method in which radiation power is generally between 0.05 and 0.5 W to avoid thermal or cytotoxic effects on tissue (Huang 2009, Sousa 2019). Low-power laser is an efficient agent for attenuating salivary hypofunction (Gonelli, 2016).

Laser and LED light induce a photobiomodulation (PBM) effect that is used to accelerate healing by increasing cell viability by stimulating ATP synthesis by mitochondrial photoreceptors and the cell membrane (Dompe, 2020). Wavelength of 810 nm can be absorbed by the chromophore cytochrome c-oxidase and other chromophores to improve mitochondrial activity. The cytochrome c-oxidase activity increases the accumulation of mitochondrial activity, which leads to greater ATP production. (Wang, 2017)

Studies have shown that photobiomodulation has been widely used to improve the functionality of the major salivary glands, as well as salivary flow. Different in vivo protocols react differently to light depending on various radiometric parameters and systemic condition (Loncar, 2011; Fidelix, 2018)

Despite different photobiomodulation methods, it is known that modified ILIB (Intravascular Laser Irradiation Blod) therapy has been studied since 1981 by Soviet scientists (Karu, 1998). The proposal with ILIB was the control of cardiovascular physiology, through the delivery of red laser therapy (660nm), through an optical fiber in the arteries or vessels, crossing the skin and introducing it into the blood vessel to, there, deposit the irradiation of a laser with 3 to 5mW of power for 20 to 30 minutes. Researchers realized in 1981 that in the heart attack area, sudden deaths decreased, because red laser therapy had probably photo-switched off nitric oxide from hemoglobin molecules and thus induced relaxation of the vessel walls and improved blood flow and tissue oximetry. The wavelength chosen for intravenous irradiation will influence the benefits reaped. Irradiation in the infrared spectrum (above 800 nm) accelerated the release of oxygen, while wavelengths between 630-670 nm promoted improvement in the transport of oxygen from the blood (Xu, 2015).

The change in the name of ILIB to Vascular Systemic Photobiomodulation (Hamblin, 2016), is more suitable for the process where light sources, lasers or LEDs, are used to deposit photonic energies, previously determined, on the skin, in the place where large blood vessels (arteries or veins) have their greatest projection towards the skin, and then evolving towards transmucosal applications, where we find a large concentration of blood vessels, that is, in the intranasal region and/or the mouth floor – sublingual.

Vascular photobiomodulation therapy promotes the absorption of red wavelength light by the blood, causing an increase in metabolism and synthesis of the enzyme superoxide dismutase, the main physiological protein regulating the body's oxidative system. Superoxide dismutase inhibits the action of reactive oxygen species (ROS), leads to the protection of cells against mutations by fighting free radicals. Therefore, the therapy aims at the functional recovery of the antioxidant enzymatic system, maintaining the balance of the organism as a whole, providing functional optimization of each system (Chamusca, 2012).

PBM to stimulate salivary production by the glands is not yet a consensus in the literature (Sousa, 2019), however there are already studies that report a significant increase (Gonelli 2016; Saleh, 2014, Loncar, 2011), and PBM in the salivary glands is safe, well tolerated and there are no reports of incidents or deleterious effects of the therapy (Sousa, 2019).

Furthermore, vascular photobiomodulation directly or indirectly affects an organism's immune cells, hormones, and metabolic processes, thereby improving not only the function of the vascular system, but also the body's other systems (Mikhaylov 2015).

One of the side effects of medications indicated for psychiatric treatment is hyposalivation or xerostomia. In search of treatments to reduce discomfort, PBM is one of the alternatives that has proven to be effective. This article aims to demonstrate the clinical improvement of a patient with severe xerostomia after treatment with vascular PBM, so that further studies in the area are possible and dosimetric parameters are defined.

**CASE REPORT AND DISCUSSION**

A patient, female, 55 years old, sought care reporting intense dry mouth. The patient reported that she always had the symptom of xerostomia, but the condition worsened after undergoing psychiatric treatment with the combination of the drug Fluoxetine Hydrochloride 20mg. The patient was already using the drugs daily: Simvastatin 20mg and Fenofibrate 200mg. When contacting the Postgraduate Program in Medicine – Biophotonics, at Nove de Julho University, the patient was referred to the clinical trial: “Effect of photobiomodulation on flow, pH and salivary immunoglobulin level in individuals with xerostomia: controlled clinical trial and randomized”. Etthics Committee - number: 5.305.375

The participant was instructed to swallow before collection and then instructed not to swallow, allowing the saliva to flow between the lips (which will be separated) into a test tube (aspirator) connected to a 15 mL Flacon tube positioned close to the mouth (Navazesh, Christensen,1982). Collection time was 5 minutes. Saliva volume was measured and salivary flow rate determined (mL/min) (Vieira, 2018). An aliquot (1 mL) of saliva was immediately transferred to a small tube (capacity: 5 mL) and a pH meter (Procyon 720 A, Procyon, São Paulo, Brazil) was used (Garcia, 2009; Vieira, 2018).

During the clinical examination, no oral and/or dental changes were observed that could compromise the smooth progress of the treatment. A specific anamnesis was taken and a questionnaire on xerostomia was administered (Table 1), in which the patient scored 28. The patient was then selected through a randomizer.org draw for group B.

|  |
| --- |
| XEROSTOMIA |
| Questions: | never | sometimes | always |
| 1 | Do you drink some liquid to help swallow the food? |  |  |  |
| 2 | Do you feel your mouth is dry during meals? |  |  |  |
| 3 | Do you get up at night to take liquids? |  |  |  |
| 4 | Do you feel dry mouth? |  |  |  |
| 5 | Do you have difficulty eating dry foods? |  |  |  |
| 6 | Do you eat candy or treats to relieve dry mouth? |  |  |  |
| 7 | Do you have difficulty swallowing certain foods? |  |  |  |
| 8 | Does your face feel dry? |  |  |  |
| 9 | Do your eyes feel dry? |  |  |  |
| 10 | Do your lips feel dry? |  |  |  |
| 11 | Does the inside of your nose feel dry? |  |  |  |
|  SCORE: |
| ANSWER OPTIONS: NEVER = 1; SOMETIMES = 2; ALWAYS = 3. |

Table 1 – Xerostomia Questionnaire

The therapeutic protocol to perform photobiomodulation was defined as: Diode laser (EccoFibras®, Campinas, Brazil), with a beam area of approximately 0.04 cm2, wavelength of 660nm and power of 100mW, delivering energy of 180J for 1800 seconds at a single irradiation point in contact with the patient's wrist (Figure 1).



Figure 1 – ILIB in position for vascular photobiomodulation enforcement.

After collecting samples for the first phase and a single session of vascular photobiomodulation, the patient got in touch reporting an improvement in the xerostomia symptom for up to 5-7 days and expressing her interest in continuing the experimental treatment.

The first irradiation and collect was in 08/03/2023, subsequently, the patient then underwent PBM on the following days: 08/03, 15/03, 22/03, 29/03, 11/04, 18/04, 28/04, 03/05, 10/05, 19/05, 25/05, 01/06 e 07/06.

Pre-irradiation salivary collect were performed to quantify the cumulative effect of the benefit of vascular photobiomodulation.

|  |  |  |
| --- | --- | --- |
| Collection Day | Flow (ml) | pH |
| 08/03 pre-irradiation | 0,2 | not possible to measure |
| 08/03 immediate post irradiation  | 0,9 | 7 |
| 08/03 30 min post Irradiation  | 0,9 | 7 |
| 15/03 after 7 days | 1 | 7 |
| 18/04 pre-irradiation | 1 | 7 |
| 10/05 pre-irradiation | 1,2 | 7 |

Table 2 – Salivary Sampling.

The parameters used in photobiomodulation are important to achieve the expected result. In the present report, the patient showed improvement in symptoms with vascular photobiomodulation at the red wavelength (660nm), although infrared in direct local application under the salivary glands is usually indicated in cases of xerostomia. This result is in agreement with studies that demonstrated the systemic action of vascular photobiomodulation (Lizarelli, 2023; Mikhaylov, 2015).

Further to the wavelength, other parameters are important such as the power, which was 100mW, the energy per point which was 180J and the equipment beam area (0.04 cm²). It’s important to note that all parameters must be informed so that clinicians and readers know exactly what treatment was performed and that, if they so wish, they can reproduce the same protocol with their patient. The number of irradiations must also be questioned. There are no reports in the literature in which the effect of the benefit of photobiomodulation is sustained for more than 7-10 days, however the ideal minimum interval time still needs to be defined (Abueva, 2022; Sousa 2019; Brzak, 2018).

Many authors report in their studies a reduction in xerostomia and an improvement in salivary flow, pH, IgA content and saliva buffering capacity. Some studies claim that PBM is able to regenerate salivary gland tissue (Plavnik, 2003A review suggests the effectiveness of PBM in the treatment of xerostomia (Sousa, 2019). A study in humans observed the effects of PBM on salivary glands of patients with xerostomia, where the authors used different parameters, infrared laser λ = 830 nm and red laser λ = 685 nm, and found an improvement in flow in both, being even better in patients treated with λ = 830 nm, this effect was observed in the long term, suggesting a regenerative effect on the salivary glands (Brzak, 2018). However, there is not enough evidence to support the claim of a cumulative or regenerative effect of PBM in a general sense, as studies were carried out on few patients or without control groups (Golez, 2022).

Close communication between the dentist (who has to deal with adverse effects) and the prescribing physician is necessary to obtain the best outcome for the patient (Wolff, 2017). Although xerostomia was a commonly reported outcome, objectively measured salivary flow rate was rarely reported. Furthermore, xerostomia was assessed primarily as an adverse effect rather than the primary outcome of medication use. (Wolff, 2017).

In this clinical case presented, the patient's psychiatric treatment is not expected to end, so the protocol is now applied in a preventive manner and not just to cure the symptoms. Studies have observed a cumulative effect of salivary gland repair when locally irradiated. With the prevention of xerostomia, the patient achieved a clear increase in her quality of life, reported by herself with the following words:

“Dry mouth can’t be resolved even with water, but the laser has improved it a lot. I stayed really well for a week, I was fine for several days, so much so that I couldn't wait to do it again, because I was feeling good and wanted to stay well”.

At each session, the patient reported a reduction in symptoms, which encouraged her to attend, as she noticed that she no longer needed to wake up to drink water. With the prevention of xerostomia, the patient achieved a clear increase in her quality of life, demonstrating that vascular photobiomodulation can be an interesting low-cost non-invasive treatment.

The effect of laser exposure was demonstrated not only in fluids subjected to direct irradiation, but also in fluids from organs located far from the irradiation zone, providing evidence of one of the potential mechanisms behind the proven systemic effect of PBM (Mikhaylov, 2015).

In a systematic review, it can be concluded that there is sufficient evidence about the beneficial effect of PBM on unstimulated salivary flow and other salivary parameters. However, there is not enough evidence to prove that the effects of PBM are long-lasting enough to improve patients' quality of life (Golez, 2022).

It was observed that laser therapy has good acceptance in the dental field, where it has been widely used in xerostomy conditions, due to its positive tissue biomodulation effects (Loncar, 2011). The advantages of PBM known to date include improvement in epithelial cell mitosis, enlargement of salivary ducts and stimulation of protein synthesis in submandibular glands (Abueva, 2022), in addition to low-intensity laser therapy being effective in reducing mucosal inflammation. oral, being important in the treatment of hyposalivation (Oliveira, 2022).

 **CONCLUSION**

Based on the protocol used in this clinical case, PBM was effective in treating the symptoms of medicinal xerostomia, increasing the quality of life of the patient undergoing psychiatric treatment using the medication Fluoxetine. Although the field is still under construction, evidence from clinical experiences can build an important track record of applications. However, further studies in the form of randomized controlled clinical trials with adequate samples are needed to confirm the findings of this case report, and in vitro studies are needed to evaluate the exact mechanism involved in PBM and salivary glands.

Abbreviations: ATP: adenosine triphosphate; PBM: photobiomodulation; LLLT: low level light therapy; ROS: reactive oxygen species; nm: nanometers; mW: milliwatts; mL: milliliters; min: minutes; J: Joules; LASER: light amplification by stimulated emission of radiation;

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