Original Research Article

PRELIMINARY OUTCOME OF IMMEDIATE EFFECT OF PHOTOBIOMODULATION ON pH AND SALIVARY FLOW

ABSTRACT

Xerostomia, a common side effect of radiotherapy, can significantly impact patients' quality of life. This study aimed to compare the immediate effects of infrared light photobiomodulation on salivary flow and pH in individuals experiencing xerostomia. Twenty adults with xerostomia participated in the study, divided into two groups: Group 1 (G1) received extraoral photobiomodulation treatment, and Group 2 (G2) received both intra and extraoral treatment. Stimulated saliva was collected before and immediately after light application. In G1, the photobiomodulation was applied using a cluster (808 nm, 120 mW, 24J), while G2 received treatment with a pointer (808 nm, 100mW, 6J per point). The results confirmed our hypothesis, showing a statistically significant increase in immediate salivary flow stimulation with the headgear technique (G1) (p= 0.037). Analyzing the percentage of volume variation (ml) per minute, the average salivary flow increased from 0.86 ml/min to 1.2 ml/min after extraoral application with an infrared laser cluster, representing a 7% increase. In conclusion, the protocol involving only extraoral application was effective in stimulating salivary flow. Further research is needed to understand the specific mechanisms behind these differences and optimize photobiomodulation techniques for xerostomia management**.**

Keywords: salivary flow; photobiomodulation;hyposalivationon; low power laser; salivary pH; xerostomia.

INTRODUCTION

Xerostomia, also known as patient-reported subjective oral dryness, is a common side effect of cancer therapies, particularly radiation therapy in the head and neck region [1, 2]. It influencesthe quality of life, counting oral infection, caries, poor sleep quality [3–5].

Dry mouth is a prevalent symptom in the general population, estimated between 21% and 27%. In a study of 197 terminally ill cancer patients, it affected 77% of them. Research on dry mouth was mostly centered on healthy patients, those with Sjögren's syndrome, or those who had received head and neck radiotherapy, leading to it being considered an overlooked aspect of supportive care. In a study on advanced cancer patients, 78% of 120 participants reported dry mouth as the fourth most common and third most distressing symptom. Most patients experienced dry mouth frequently, and severity was often rated as moderate, severe, or very severe[1].

Saliva is a body fluid of complex composition that guarantees the health of the oral cavity. It originates from 3 pairs of major salivary glands: the parotid, submandibular and sublingual glands, and from numerous minor salivary glands located in the oral mucosa [2]

Saliva allows lubrication and humidification of the oral cavity and associated structures, due to its viscosity and elastic properties. Among some of its functions, we can mention: its importance in swallowing, through the formation of a cohesive food bolus and the unimpeded passage of the food bolus to the digestive tract; its performance in phonation, due to its lubricating property, and due to its

buffering capacity, it acts in an important way in the modulation of remineralization and demineralization of the dental structure[2–4]

There is a high prevalence and/or incidence of caries among people with pathologically low salivary flow, compromised buffering capacity, and early colonization or high titer of *Streptococci mutans* in saliva[5]. Pyati et al (2018) found that the significant change in salivary flow rate, pH and total protein levels in active children with caries suggest that the levels of these physicochemical properties of saliva can act as strong indicators of caries status. in children[4].

Components such as sodium, calcium, magnesium ions, chlorine, bicarbonate, inorganic phosphate, ionic strength, and even pH, among others, may change due to increased salivary flow [2]

In addition to its physiological functions, saliva is a useful biological fluid in the diagnosis of diseases. Its composition includes enzymes, antibodies, bacteria, viruses, electrolytes, proteins, and other components, which is why saliva has been shown to be an excellent alternative for clinical analysis [3]

Phototherapy is a treatment with different modalities of light sources, such as laser, light emitting diode (LED) light, halogen light, or others[6]

To better understand the effects of photobiomodulation on cells, the theory that photobiomodulation reacts with target cells photochemically is cited. ((Freitas et al., 2016). This theory says that mitochondria contain chromophores that absorb photons from the PBM. The primary chromophore to absorb red light is the enzyme cytochrome c oxidase, which is located in unit IV of the mitochondrial respiratory chain, resulting in the activity of various molecules such as nitric oxide (NO), ATP, calcium ions, reactive oxygen species (ROS), and several other signaling molecules [7,8]. Glycolysis and ATP production are thought to be promoted due to the stimulation that PBM causes the electrons in the chromophores to move from higher energy orbits and, immediately, the electron carriers (such as the chromophore, cytochrome, and oxidase) deliver these electrons to their final electron acceptors while a proton gradient is made, in addition to creating a proton gradient which increases ATP production. In addition, several transcription factors are activated by PBM [7,9–11]

In dentistry photobiomodulation has been found to be effective in relieving the side effects of cancer treatment, relieving pain, alleviating the symptoms of Sjogren's Syndrome , reducing the amount of periodontal pathogenic bacteria, stimulating the salivary glands, increasing regeneration of undamaged glandular tissue after cancer irradiation, improving saliva properties, and acting on salivary rate in hyposalivation[11–13](Carroll et al., 2014; elMobadder et al., 2019; Fidelix et al., 2018).

The literature shows the effects of low-level laser therapy on the salivary glands are not only stimulating but also regenerative to a certain degree, since the glandular response to the same amount of laser energy applied increased linearly with the time[15,16].

In the study by Nemeth et al. (2020), where the aim of the prospective randomized study was to verify how photobiomodulation of the major salivary glands, with polychromatic light or LED light, affects caries risk factors, in adult patients with high caries risk, where the risk factors caries were determined from saliva samples before therapy, two weeks after initiation, at the end of therapy and four weeks after the end of therapy; it was concluded that photobiomodulation of the major salivary glands in

patients at high risk of caries can reduce cariogenic bacteria in saliva and improve some salivary parameters, thus reducing the risk of caries[17].

Studies show that there was an increase in salivary flow after the use of low-level laser [12,15], and an increase in salivary pH with the use of LED[17] but , studies such as the one by Louzeiro et al(2020) [18]where the effects of photobiomodulation on the salivary glands of patients undergoing head and neck radiotherapy were evaluated, and the study by Fidelix et al[13,14]which evaluated the action of low-intensity laser in Sjogren's Syndrome patients did not find improvements in salivary parameters. However, as in these two studies the salivary glands were compromised, the authors considered that this fact influenced the results.

Knowing the importance of salivary parameters being in balance for: maintenance of health in the oral cavity; adequate phonation and digestion. Considering that adequate salivary flow and pH are important in protecting teeth. Knowing that the use of photobiomodulation in salivary glands, are controversial in the measurement of flow and pH, in specific cases, where the salivary glands are not in its perfect functioning. And, considering the study of Bzark et al. [15] who concluded improvement in salivary parameters with the use of infrared laser compared to red laser. The present study aims to evaluate and compare the immediate effect on pH and salivary flow with intraoral and extraoral photobiomodulation and only extraoral infrared laser on the salivary glands of adult subjects.

METHODOLOGY

Study location and sample selection

The study was carried out with 20 participants with xerostomia at the Nove de Julho University and was conducted in compliance with the regulatory norms that govern research involving human beings, with approval by the research ethics committee with opinion number 5,305,375, the participants expressed their agreement to participate in this study, by completing and signing the informed consent form, clinical trial registration NCT05413993

The sample design was based on the study by Marín et al. (Marín et al., 2021) using the GPower software version 3.1 (Universitat Kiel, Germany), which reached a total sample size of 15 participants per group, considering possible losses, 20 adults were recruited for the study. A convenience sample was used. Participants were recruited by face-to-face invitations at Universidade Nove de Julho and locations close to the University. This study followed the CONSORT recommendations of the EQUATOR network publication guidelines (http://www.equator-network.org).

Inclusion criteria

Adults over 18 years of age with healthy dentition and xerostomia

Exclusion criteria

Participants with compromised health and who have teeth with caries, gingivitis, or other alterations in the oral cavity, who have used an antibiotic or anti-inflammatory within the last 30 days.

Study groups.

Participants answered a questionnaire with clinical information related to dental history, medical history and the Xerostomia Inventory - XID questionnaire, which consists of a simplified form with only three response options. The answers include never (1 point), occasionally (2 points) and always (3 points). The value obtained for everyone is calculated by adding up all the points. The score can range from 11 to 33 points and the closer to 33, the greater the degree of xerostomia.

Participants received both treatments, extraoral and extra and intraoral application, with an interval of 7 days between the two procedures. In this way the participants were their own controls. For evaluation purposes, the procedure of extraoral application only of G1 (n=20) and the procedure of intra and extraoral application of G2 (n=20) were named.

Conduct and research protocol.

Saliva collection and analysis

The saliva was collected at the Dental Clinic of the Universidade Nove de Julho, with the adult seated at the dental team. To obtain the stimulated saliva, we used sialogogue chewing for 5 minutes, and the saliva collection was performed, by expectoration of all the saliva accumulated in the mouth every 1 minute of chewing, inside graduated glass tubes. Stimulated saliva was collected before and immediately after laser application. This procedure is performed both in the extraoral application only, and in the intra and extraoral application. After collection, 3 drops of simethicone were used to eliminate gases and foam, and only after this procedure the volume of saliva collected was measured.

The saliva tube was properly placed on a bench for immediate pH measurement with a colorimetric tape (MERCK ®Quimical, São Paulo, Brazil) inside the collecting device. The tape features a pH scale from 0 to 14.

Laser application protocol

G1 - extraoral application

The infrared laser was applied with the Ecco Reability equipment (Eccofibras, São Paulo, Brazil) and with the cluster with 3 spots at a wavelength of808 nanometers and power of 120 mW. 24J of energy were applied on the extraoral surface in the region of the parotid gland, region of the submandibular and sublingual glands bilaterally, totaling 4 regions of application.

G2 - intra and extraoral application

The laser was applied for 60 seconds, in 2 intraoral points and 2 extraoral points in the region of the parotid glands bilaterally, as well as 1 intraoral point and 1 extraoral point in the regions of the

submandibular and sublingual glands (totaling 16 points). The laser was adjusted according to the following parameters: central wavelength (nm)= 808 nm; continuous operating mode; power of 100mW; with opening diameter 0.354 cm (with spacer); radiant energy of 6J (Table 1).

Table 1-. Dosimetric parameters used in applications in groups G1 and G2

PARAMETERS	G1 INFRARED LASER	G2 INFRARED LASER
Wavelength [nm]	808	808
Operating mode	Continuous	Continuous
Power [mW]	120	100
Beam area [cm2]	21 cm2	0.0984 (with spacer)
Exposure time [s]	67 by region	60 per point
Fluence [J/cm2]	61	61
Energy [J]	24 by region	6 per point
Number of irradiated points	4	16
Application technique	Contact	Contact
Number of sessions	1	1
Treatment frequency	1 single application	1 single application
Total radiated energy [J]	96	96

Statistical analysis

Data were analyzed using Analysis of Variance (ANOVA) and Wilcoxon test ($\alpha = 0.05$). The Statistical Package for the Social Sciences (SPSS) (IBM Corp. launched in 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp) version 15.0 was used for all analyses.

RESULTS

The sample consisted of 20 participants, 70% (n=14) of the female gender and 30% (n=6) of the male gender. The mean age was 30.25 years (sd=9.8). Table 2 presents the characteristics of the participants in relation to their dental and medical history. When evaluating the Xerostomia Inventory,

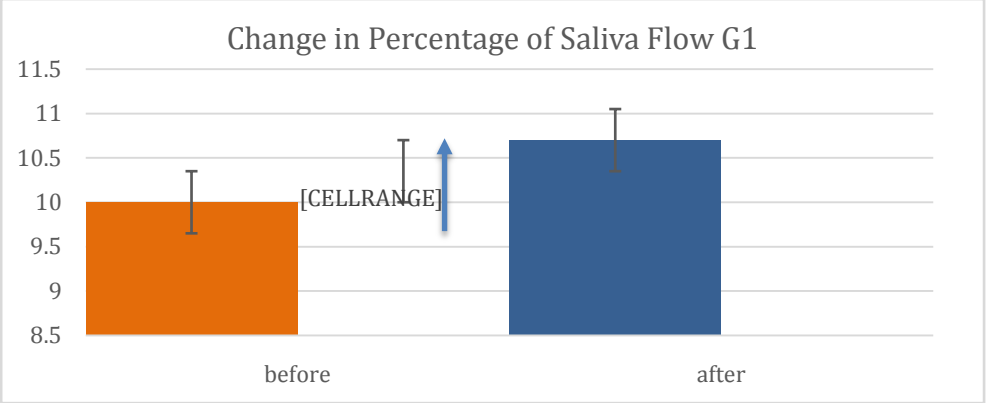
the average score of the participants was 17.55 (sd= 3.4), considering that the maximum score is 33, with the highest 25 points and the lowest 14.

Table 2. Characteristics of the participants in relation to dental and medical history.

When was your last visit to the dentist?	6 months	1 year	More than a year
	40% (n=8)	25% (n=5)	35% (n=7)
Do you regularly visit the dentist?	Yes	No	
	55% (n=11)	45% (n=9)	
Do you have any illness?	Yes	No	
	10% (n=2)	90% (n=18)	
Depression	Yes	No	
	10% (n=2)	90% (n=18)	
Are you undergoing radiotherapy or chemotherapy treatment?	Yes	No	
	0	100% (n=20)	
Do you have an eating disorder?	Yes	No	
	0	100% (n=20)	
Smoker?	Yes	No	
	30% (n=6)	70% (n=14)	

The volume of saliva of the participants during the 5 minutes was measured to calculate the salivary flow and the percentage of variation. After the initial collection of saliva, before the first application, it was found that the group that participated in this experiment presented an average of 0.86 ml/min of salivary flow rate. To verify if there was a difference in salivary flow between before and immediately after the application of photobiomodulation, the percentage of volume variation (ml) per minute was considered.

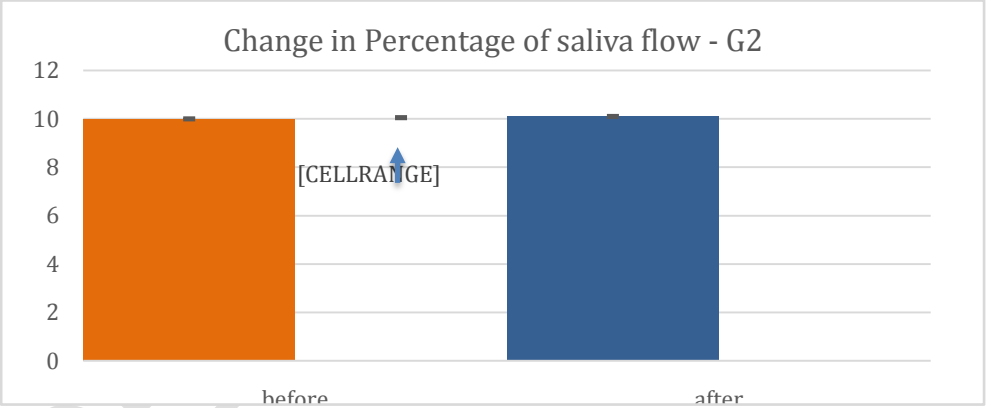
After extraoral application with an infrared laser cluster, the average salivary flow increased from 0.86 ml/min to 1.2 ml/min. This increase was 7% and was considered statistically significant compared to baseline on the same day ($p<0.05$). Figure 1 represents the volume and variation of salivary flow in G1.



* statistically significant, p<0.05, Wilcoxon test

Figure 1- Volume and variation of salivary flow after application of the extraoral infrared laser-G1

After 7 days, when the participants returned, the pre-application measurement in G2 (intra and extraoral) of the infrared laser with a tip indicated a flow rate of 1.20 ml/min. It was observed that the rate remained unchanged in relation to the previous week. However, after applying the G2 procedures, the immediate flow variation was only 1% in relation to the pre-application measure on the same day (Figure 2), with a rate of 1.22 ml/min, as shown inFigure 3. The difference between before and after in G2 was not statistically significant (p>0.05).



statistically significant, p>0.05, Wilcoxon test

Figure 2- Volume and variation of salivary flow after application of the extraoral and intraoral infrared laser-G2

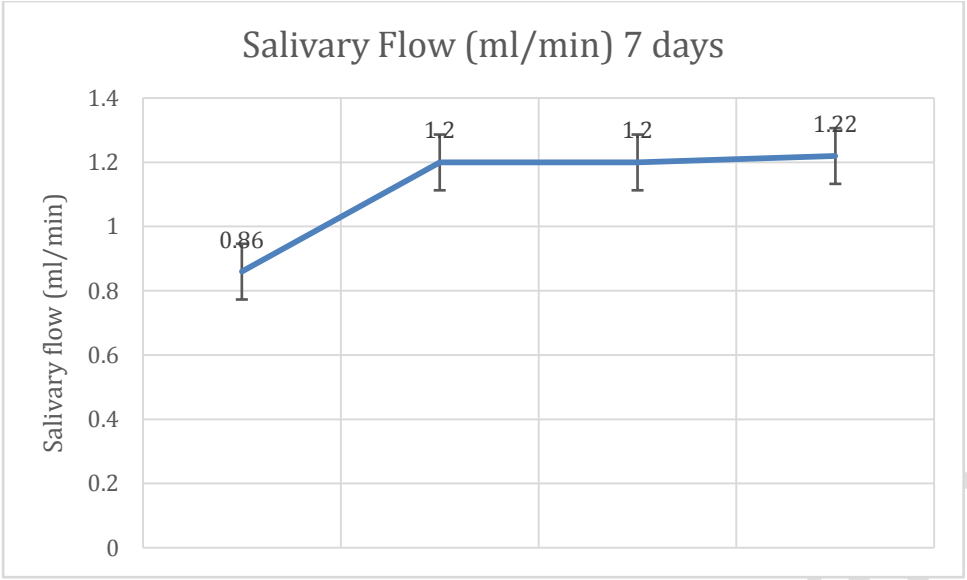


Figure 3 - Salivary flow (ml/min) in the four measurement moments.

Salivary pH analysis showed that there was no immediate change in either of the two application methods or in any of the participants. The initial average of the salivary pH at the first moment was 7.1 and immediately after the G1 application the average was 7.05. After seven days of the first application, the average pH of 7 went to 7.1 immediately after the G2 application (Figure 4). These subtle changes in pH were not statistically significant (p>0.05).

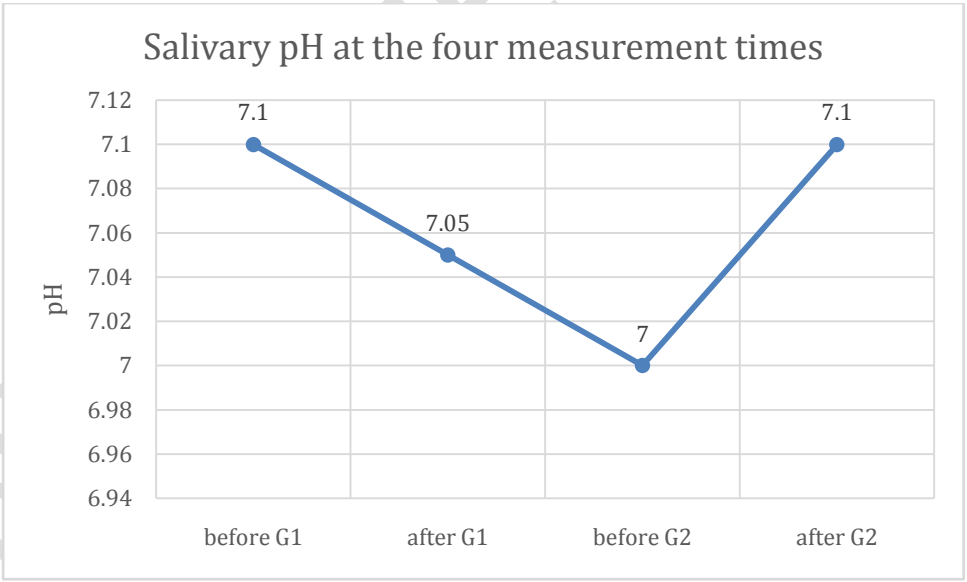


Figure 4- Mean salivary pH at the four measurement times

DISCUSSION

Saliva is essential for maintaining the health of the oral cavity. It plays a crucial role in digestive, gustatory, phonation and teeth protection functions(Biology & 2018, 2018; Kim et al., 2017; Louzeiro et al., 2020; Wang et al., 2019.; Yoshizawa et al., 2013)

There are salivary parameters that must be in balance so that saliva functions are adequate. Salivary variations, such as decreased flow, change in pH and composition, can lead to changes in oral health, such as dry mucosa with consequent dysgeusia, dysphagia and dysphonia, or risk of developing ulcerations(Louzeiro et al., 2020)

Phototherapy is a treatment with different modalities of light sources, such as laser, light emitting diode (LED) light, halogen light, or others(Abueva, 2022; Freitas et al., 2016. Photobiomodulation has been used in dentistry to relieve the side effects of cancer treatment, relieving pain, relieving the symptoms of Sjogren's Syndrome, reducing the amount of periodontal pathogenic bacteria, stimulating the salivary glands, increasing tissue regeneration undamaged glandular after cancer irradiation, improving saliva properties and acting on salivary rate in hyposalivation. However, the use of photobiomodulation to increase salivary flow and increase pH has been controversial in the literature(Carroll et al., 2014; Fidelix et al., 2018). Some studies show that there was an increase in salivary flow after the use of low-level laser [12,15], and an increase in salivary pH with the use of LED [17].

Authors who evaluated the effects of photobiomodulation on the salivary glands of patients undergoing head and neck radiotherapy(Louzeiro et al., 2020), and evaluated the action of low-level laser in patients with Sjogren's Syndrome, did not find improvements in salivary parameters. However, as in these two studies the salivary glands were compromised, the authors considered that this fact influenced the results(Fidelix et al., 2018).

The most used way of applying photobiomodulation to the salivary glands, is with the associated intraoral and extraoral technique (Abueva, 2022; Brzak et al., 2018; Campos et al., 2010; elMobadder et al., 2019; Freitas et al., 2016)

However, often, the patient in need of stimulation of the salivary glands can also suffer from other discomforts that make mouth opening difficult, such as ulcers, dryness of the labial commissure and others. Therefore, the possibility of a technique that deposits energy in the region of the salivary glands with an extraoral technique, exclusively, can bring more comfort during the procedure.

The present study aimed to compare and evaluate two types of light application techniques in the salivary glands, being Group 1, performed only the extraoral application and group 2 intra and extraoral applications, in order to evaluate and compare the immediate effect. in pH and salivary flow in these two techniques.

The satisfactory salivary flow of stimulated saliva is 1.0 to 3.0 ml/min (Tenuovo, 1997). In the present study, we observed an average flow rate of 0.86 ml/min for the stimulated saliva of the group of participants before any intervention. The literature points as a reference for hyposalivation rates below 0.7 ml/min.

There was an increase in flow immediately after the first intervention to 1.2 ml/min, within satisfactory parameters for stimulated saliva. This result showed that photobiomodulation in the parameters studied and with extraoral application was able to immediately raise the flow to satisfactory levels.

In this study, an increase in salivary flow was observed in the two techniques used, which corroborates the study by elMobadder*et al*. (2019), who found an increase in salivary flow from the first application and during the 5 photobiomodulation sessions. However, the authors used different dosimetric parameters, used laser in the red range (635 nm) and 3J/cm2 in 20 extra and intraoral points[12].

Brzak *et al*. (2018) also observed an increase in salivary flow with the use of infrared laser. In this last study, the authors compared two wavelengths, the red laser (685 nm) and infrared (830 nm) and observed an increase in the flux in the two groups with better results for the infrared. In the same study, maintenance of the flow was observed after 10 days in the group that received infrared[15]. In contrast, Louzeiro*et al*.(2020), after evaluating patients with head and neck cancer undergoing radiotherapy, found no difference in salivary flow between the group that received photobiomodulation with red laser (660 nm) and infrared (810 nm) concomitant did not differ from the placebo group(Louzeiro et al., 2020.

The differential of this research was to evaluate the application of the extraoral technique only in relation to the most common technique in the literature, which is in intra and extraoral stitches. This technique proved to be effective in increasing salivary flow. As it was an extraoral application only, and therefore with fewer stitches, it was a faster and less uncomfortable laser application, since the patient did not need to keep his mouth open for the intraoral application.

The increase in salivary flow rate increased in both groups, being statically significant in G1 immediately and maintained for 7 days. No data were found for immediate assessment of salivary flow, but in relation to maintenance, the results are in line with the findings of literature [15], wich revealed that the effect of photobiomodulation can be observed up to 10 days after completion of treatment, indicating that the effect is not only short-term. When comparing the groups studied, it was observed in this sample that there was no significant increase in the application of G2. However, in the methodology used, it was not possible to verify whether the fact that there was no increase 7 days after the first application was not related to the maintenance of the effect of the first application. It can be assumed that the participantsreached the physiological limit of production and salivary flow rate with the extraoral application. Therefore, it is not possible to say that the intraoral and extraoral technique (G2), used more frequently, has a less significant effect than the one applied only extraorally. In this context, we can reflect that photobiomodulation could restore the function of the salivary glands keeping the satisfactory flow constant, as well as having a regenerating effect on muscles, for example [15,16].

Regarding salivary pH, there was no immediate effect in the two groups studied, however, participants had a mean pH of 7 (neutral) at baseline. It is believed that photobiomodulation may be able to increase buffering activity in situations where homeostasis is compromised(Louzeiro et al., 2020) that patients undergoing radiotherapy after being treated with photobiomodulation showed an increase in salivary pH. At this point, the present study is limited for this comparison, since the salivary glands of the participants showed no alterations.

With this study, it was found that the infrared laser with a wavelength of 808 nm, applied only extraorally, with a cluster and an energy of 24J per region, was statically significant in the activation of the salivary glands to increase the salivary flow. This technique showed better results when compared

with the more conventional technique of laser application (extra and intrabuccal associated) where the parameters used were: 808 nm wavelength, applied at 16 points, with each point depositing an energy of 6 joules, totaling 96 joules of total energy.

The literature presents a variation of protocols for the use of light in the activation of the salivary glands, where parameters such as: the type of light, wavelength and total energy used, differ greatly; it is difficult to define the best protocol to be used. Therefore, further clinical studies should be performed, mainly with long-term follow-up, with larger samples and with assessment of the maximum potential for salivary production of the salivary glands after photobiomodulation. Immediate assessment studies in different groups and not in the same participants can also contribute to the elucidation of long-term pH maintenance, both in the extraoral-only and in the conventional technique.

Both the literature and the results of this research suggest the positive effect of photobiomodulation on salivary parameters and faster, more comfortable, and effective protocols need to be established with the development of clinical research.

CONCLUSION

In this study we compared two photobiomodulation application techniques to stimulate salivary glands in relation to salivary flow and pH. One of the techniques was extraoral only and the other, the more conventional, intra and extraoral with the same parameters of wavelength and total energy.

It was possible to conclude that both techniques were able to increase salivary flow, with superior results for the headgear-only technique. There was no change in salivary pH in either group and the extraoral technique was able to maintain satisfactory flow for at least 7 days.

HIGHLIGHTS

- Salivary variations, such as decreased flow can lead to changes in oral health.
- Photobiomodulation as an adjuvant in salivary treatment.
- Extraoral application of laser light promotes salivary stimulation.

Post Graduation Program in BiophotonicsMedicine, Universidade Nove de Julho, São Paulo, SP, Brazil

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Declarations

Ethics: This study was approved by the Ethics and Research Committee of our institution under protocol number 5.305.375.

Clinical Trials: NCT054139932022-06-10

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Institutional Review Board Statement: "Not applicable

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