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Complete List of Authors:	Lončar Brzak, Božana; School of Dental Medicine, Department of Oral Medicine Cigić, Livia; School of Medicine, University of Split, Department of Oral Medicine and Periodontology Baričević, Marinka; Health Care Centre Zagreb West Sabol, Ivan; Institute Rudjer Bošković Stipetić, Marinka; School of Dental Medicine, Department of Oral Medicine Risović, Dubravko; Institute Rudjer Bošković, Laboratory of Molecular Physics
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Different protocols of photobiomodulation therapy of hyposalivation

Božana Lončar Brzak[1], DMD, PhD; Livia Cigić[2], DMD, PhD; Marinka Baričević[3], DMD, PhD; Ivan Sabol[4], PhD; Marinka Mravak-Stipetić[1], DMD, PhD; Dubravko Risović[5], PhD

[1] Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia

[2] Department of Oral Medicine and Periodontology, School of Medicine, University of Split, Split, Croatia

[3] Health Care Centre Zagreb West, Zagreb, Croatia

[4] Department of Molecular Medicine, Ruđer Bošković Institute, Zagreb, Croatia

[5] Molecular Physics Laboratory, Ruđer Bošković Institute, and Centre of Excellence for Advanced Materials and Sensing Devices, Zagreb, Croatia

Running title: Photobiomodulation protocols for hyposalivation

Corresponding author:

Professor Marinka Mravak Stipetić, DMD, MSc,PhD

Department of Oral Medicine, School of Dental Medicine

University of Zagreb

Zagreb, Croatia

mravak@sfzg.hr

phone: +38514802114

Aim

Photobiomodulation (PBM~~T~~) therapy has proved to be effective for a wide range of oral pathologies including oral dryness, but the literature still lacks reports of clinical trials and protocols. The purpose of our study was to evaluate the effects of different wavelengths of PBM~~T~~ on salivation in patients suffering from hyposalivation aiming at determination of optimal treatment protocol.

Materials and methods

This study included 30 patients whose major salivary glands were treated with low intensity diode laser BTL2000 (Medical Technologies, s.r.o., Czech Republic) during 10 consecutive days. Patients were randomly assigned in two groups, each of 15 patients, and treated with PBM~~T~~ of 830 nm and PBM~~T~~ of 685 nm, respectively. The whole unstimulated and stimulated saliva was measured each day during 10 days, before and after laser treatment and 10th day after treatment was ended.

Results

Results have shown that the laser treatment significantly improves salivation ($p<0.0001$) in both groups after 10-days treatment. The salivation also remains improved 10 days after the end of the treatment. The patients treated with PBM~~T~~ of 830 nm have had continuously higher values of quantity of saliva.

Conclusion

Our results have shown that both laser wave-lengths were effective in increasing salivary flow rate, and the improvement in salivation was statistically significant. The effect of treatment could be observed 10 days after the completion of the treatment thus providing

evidence not only of stimulative effect but also indicating regenerative potential of photobiomodulation therapy.

Introduction

Xerostomia is an often complaint mainly in elderly population, resulting with difficulties in speaking, food swallowing and tasting, denture wearing, burning sensations in the mouth and increased susceptibility of oral mucosa to diseases[1]. Although the lack of saliva seriously impairs the quality of life, it is often neglected. Etiology of xerostomia is different, varying from salivary gland disease, systemic diseases, radiation therapy or, the most frequently, drug-induced xerostomia[2–5]. Increasing salivary flow (in case acinar cells are preserved) represents the best therapy, but gustatory stimulation is short-acting and must be often repeated[6,7]. Other therapeutic models include use of systemic sialogogues, electrical stimulation, acupuncture[3], and use of saliva substitutes[5]. Each of these methods has some limitations, as described in our previous work[8]. Many different artificial saliva products on the market are of limited value in the treatment of xerostomia. Although convenient and simple, some patients find gustatory stimulation debilitating and tiresome. Systemic cholinergic agents such as pilocarpine and cevimeline increase salivary flow rate, but have side effects and certain contraindications[5].

Low level laser treatment, more recently termed photobiomodulation (PBM), has proved to be effective for a wide range of oral pathologies including oral dryness, but the literature still lacks reports of clinical trials and protocols. Photobiomodulation (PBMT) therapy induces changes in the cellular redox state and pH homeostasis[9], increases ATP production in the cell[10,11] and converts laser light energy input through biochemical and photophysical processes into energy useful to the cell[12].

In our previous study [8] we have reported the efficacy of PBMT for the treatment of xerostomia providing good therapeutic results. Since then, we have introduced a new laser device and performed research with two different wavelengths in patients with hyposalivation. The aim was to evaluate the effects of these new laser wavelengths, different from those used in previous research, on salivation of patients suffering from hyposalivation. This with purpose to possibly find the optimum laser wavelength for the treatment, and to determine the better protocol for the patients suffering from hyposalivation.

Materials and methods

The study included 30 consent female patients (age range 52-85y, mean age 69.6, median 72) whose major salivary glands were treated with low intensity diode laser (BTL-2000 Medical Technologies, Prague, BTL Co., Czech Rep.). The nominal output of the probes were 30 mW at 685 nm and 100 mW at 830 nm and set at a pulse repetition rate of 5.2 Hz to deliver 30 mW at 685 nm and 35 mW at 830 nm. The power measurements were provided by the manufacturer. ~~operating in a pulse mode at a frequency of 5.20 Hz and delivering a 30 mW power output at 685 nm and 35 mW power output at 830 nm.~~ The treatment was performed during 10 consecutive days, with a laser probe. During application, protective eyeglasses were worn both by the operator and the patient. The patients were divided in two groups; the first group comprised 15 female patients (age range 52-77 years, mean age 69.53, median 72) which were treated with 830 nm laser wavelength. The second group comprised 15 female patients (age range 55-85 years, mean age 67.67, median 72) which were treated with 685 nm laser wavelength. To establish the diagnosis of hyposalivation, the amount of total unstimulated saliva was measured at the initial examination of the patients. After that the salivation was stimulated with citric acid. Photobiomodulation therapy was not started at the initial examination of the patient to avoid any possible error in the measurement of saliva quantity after different types of stimulation. The photobiomodulation therapy began on the next day.

The total unstimulated and stimulated saliva quantities were measured before and after each laser treatment and 10 days after the last (10^{th}) treatment, to determine the durability of results. Patients were asked to expectorate all saliva into graduated test tubes for a 5-min period. The amount of saliva was determined by the scale on the graduated tubes.

The inclusion criteria for all patients were medical histories free of radiotherapy and Sjögren's syndrome. Sjögren's syndrome was excluded by the applied diagnostic criteria[13]. In all patients clinical examination and sialometry was done and anamnestic data (drug history) were taken. Our research was approved by the Ethical Committee of our faculty and registered at U.S. National Institutes of Health (trial identifier: NCT03049943). All patients signed informed consent to participate in the study.

The laser beam was applied bilaterally to each salivary gland area, extraorally to the parotid and submandibular glands and intraorally to the sublingual gland (each patient received a total of six exposures, each of different duration depending of the gland and laser wavelength which was predetermined by the laser settings. The treatment lasted for 10 consecutive days. The distance between the probe and the irradiated area was kept constant at 0.5 cm throughout the treatment period. The spot size was difficult to calculate due to slight difference from the irradiated area so it was estimated. The laser probe was not held stationary, but moved around in mesh-shaped movements. This technique is recommended for manual scanning to ensure that a reasonably uniform dosage is delivered to all areas of the treated surface[14]. The relevant technical data for the photobiomodulation therapy are given in Table 1.

Statistical methods, including correlation analysis, t-test and repeated measures ANOVA (with Bonferroni's multiple comparison post-hoc test) were used for comparison and interpretation of the difference in salivary flow rates between the two groups.

Results

The average salivary flow rates obtained from the both laser wavelength groups before and after PBMT throughout the 10-day treatment period and 10 days after the last (10th) treatment are shown in Figure 1. If we compare the results by the laser wavelength, we can see that the patients in the 830 nm laser wavelength group have higher values of saliva stimulation throughout the study than the patients in the 685 nm laser wavelength group.

The comparison of average measured salivary flow rate before the laser treatment on the first day with that on the last day of the treatment series shows significantly higher rate for both laser groups of patients and for all patients (*T-test for paired examples*, $p = 0.0044$ (685 nm), $p = 0.0019$ (830 nm), $p<0.0001$ (all patients)) (Fig. 2.). Also the comparison of average measured salivary flow rate before the laser treatment on the first day with that measured 10 days after the end of the treatment, shows that the salivation was significantly increased for all patients (*T-test for paired examples*, $p=0.0009$) and each group of patients ($p = 0.0121$ (685 nm), $p = 0.0347$ (830 nm)) (Fig. 3.). The results were also statistically significant by repeated measurements ANOVA testing (all patients $p<0.0001$; 685 nm laser $p=0.001$; 830 nm laser $p<0.0001$). However, Bonferroni's multiple comparison post test only confirmed the significance of salivary flow rate differences between the first day and last day of the treatment for 830 nm laser ($p<0.01$). The difference between first day and 10th day after treatment did not reach statistical significance together with same comparisons for 685 nm laser.

Discussion

Our results show that treatment with both laser wavelengths, 830 nm and 685 nm, was effective in improving the salivary flow rate. After ten days of treatment in each treated group of patients the average salivary flow rate was significantly higher. The treatment with wavelength of 830 nm was more effective resulting in a higher average increase of salivation. The observed difference in efficiency of 830 nm and 685 nm (at the same applied energy level) could be attributed to different spectral absorption properties of the oral soft tissue's main chromophores, in particular water and oxyhemoglobin. Namely, the absorption coefficient of water (comprising about 75% of the tissue) is approximately five times higher at 830 nm than at 685 nm while for oxyhemoglobin the difference in absorption coefficients is about 25%[15,16].

By comparing the differences in saliva stimulation in each group for 10 consecutive days of treatment, we can see that the response of the gland to the same amount of applied energy was not constant. Unlike our previous study[8], we didn't observe linear increase in salivation flow during the treatment. Rather, after initial significant increase in first few days of treatment, it remained, with slight oscillations, at a relatively constant value. The salivation in both groups on the last day of treatment and 10 days after the end of the treatment was improved, in comparison to the unstimulated whole saliva at the first day of treatment before beginning of ~~photobiomodulation~~ PBM therapy, and this difference is statistically significant. The salivation remained improved for prolonged time as documented with measurements accomplished ten days after the end of treatment. This improvement in the salivation rate, although somewhat lower than the increase observed during the treatment, is important because it indicates that this type of therapy does not have only short-term effect, but has also the regenerative effect on salivary glands as their function remains restored for a certain time after the completion of the therapy. In recent years, the regenerative effect of PBM~~T~~ was described in the literature for treatment of muscle repair[17,18], wound healing[19,20], mesenchymal stromal cells therapies[21] and xerostomia[8]. Our results also confirm the biostimulative and regenerative effect of PBM~~T~~, due to restoring salivary glands function, which remained improved at least ten days after the termination of the ~~photobiomodulation~~ PBM therapy. In this context it would be intriguing to see whether an occasional ~~photobiomodulation~~ PBM therapy would help to maintain the achieved amount of salivation on constant level, which would be a great advantage of this type of hyposalivation treatment.

Regarding the effects of medication on salivation in the literature one can find many studies reporting decrease of salivary flow rate due to use of various drugs[2,22-24]. Since all of our patients were taking medication for their other health conditions, we could assume that the xerogenic effect of the used drugs, with prolonged time after the completion of the therapy inhibits salivation, causing hyposalivation. Despite this possible negative influence of used drugs our investigation proved the effectiveness of the 830 nm and 685 nm photobiomodulation therapy in stimulation of salivation.

Since the world population of elderly people is increasing and polytherapy (taking multiple medications) is becoming more and more frequent in general population, it is important to find efficient therapy for hyposalivation which doesn't have side effects and gives the best results. In this context it is important to emphasize that none of the patients included in this study reported any side-effects from this type of therapy. Literature offers many positive results of photobiomodulation for treatment of decreased salivary flow rate[8,25–29], but with different laser parameters and treatment protocol. Searching the literature, we didn't find published research on patients with hyposalivation similar to ours, so we could not compare our results with those from other studies. In comparison with our previous study where we have applied 904 nm wavelength on salivary glands[8], along with these results, we can confirm better therapeutic response of wavelengths in infra-red part of spectrum.

Conclusion

We have investigated the effects of PBMT with wavelengths 830 nm and 685 nm on salivation in patients suffering from hyposalivation.

Our results have shown that both laser wavelengths with selected exposure times were effective in increasing salivary flow rate, and that the improvement in salivation was significant. Although the difference between the two laser groups was not statistically highly significant, the 830 nm laser wavelength proved to be more effective in stimulating the salivation. This difference could be attributed to the different spectral absorption properties of the oral soft tissue's main chromophores. The positive effect of the photobiomodulation therapy could be observed 10 days after the completion of the treatment, with better maintained effect of 830 nm wavelength. Thus, indicating a regenerative potential of this type of therapy which should be further investigated and compared with other therapeutic options for hyposalivation.

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Author Disclosure Statement

No competing financial interests exist.

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Reprint requests should be directed to:

Professor Marinka Mravak Stipetić, DMD, MSc,PhD

Department of Oral Medicine, School of Dental Medicine

University of Zagreb

Zagreb, Croatia

mravak@sfzg.hr

phone: +38514802114

Table 1. The relevant technical data for the laser therapy

Salivary gland	Laser specifications	685 nm	830 nm
parotide gland	Dose (J/cm^2)	1.80	1.80
	Power (mW)	30	35
	Area (cm^2)	4.00	4.00
	Applied energy (J)	9	8.995
	Power density (W/cm^2)	0.0075	0.00875
	Distance (cm)	0.5	0.5
	Time (m:s)	5:00	4:17
	Max. power (mW)	30	35
	Frequency (Hz)	5.20	5.20
	Number of treatments	10	10
	Cumulative dose given (J/cm^2)	18.0	18.0
submandibular gland	Dose (J/cm^2)	1.80	1.80
	Power (mW)	30	35
	Area (cm^2)	1.60	1.60
	Applied energy (J)	3.6	3.605
	Power density (W/cm^2)	0.01875	0.021875
	Distance (cm)	0.5	0.5
	Time (m:s)	2:00	1:43
	Max. power (mW)	30	35
	Frequency (Hz)	5.20	5.20
	Number of treatments	10	10
	Cumulative dose given (J/cm^2)	18.0	18.0
sublingual gland	Dose (J/cm^2)	1.80	1.80
	Power (mW)	30	35
	Area (cm^2)	0.80	0.80
	Applied energy (J)	1.8	1.785
	Power density (W/cm^2)	0.0375	0.04375
	Distance (cm)	0.5	0.5
	Time (m:s)	1:00	0:51
	Max. power (mW)	30	35
	Frequency (Hz)	5.20	5.20
	Number of treatments	10	10
	Cumulative dose given (J/cm^2)	18.0	18.0

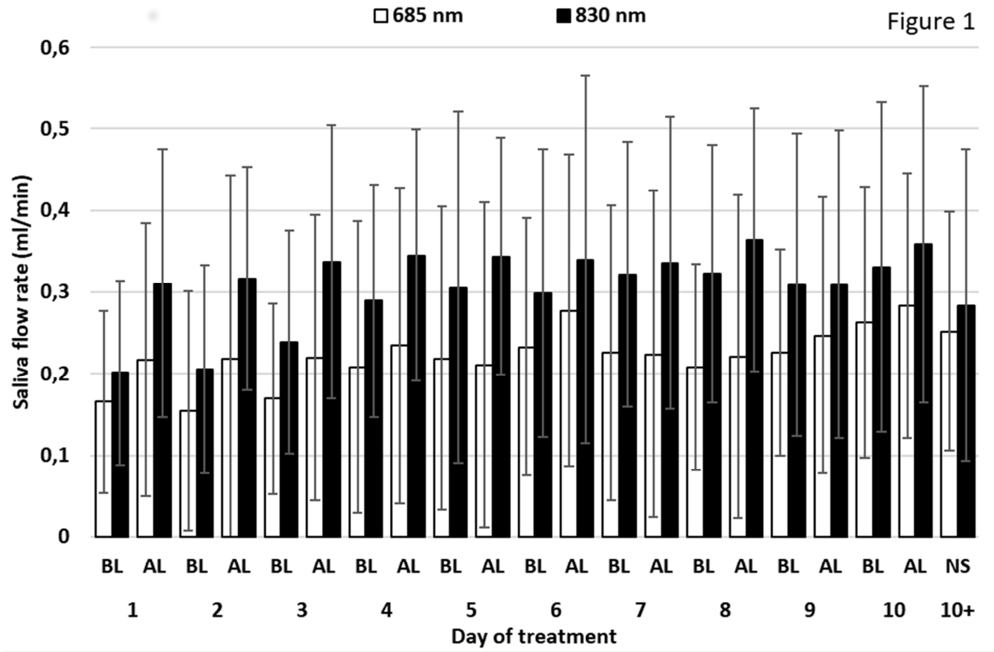

Figure 1. Average measured mean saliva flow rate in groups treated with different lasers: BL= before the laser treatment, AL= after the laser treatment and 10 days after the completion of treatment series (NS).

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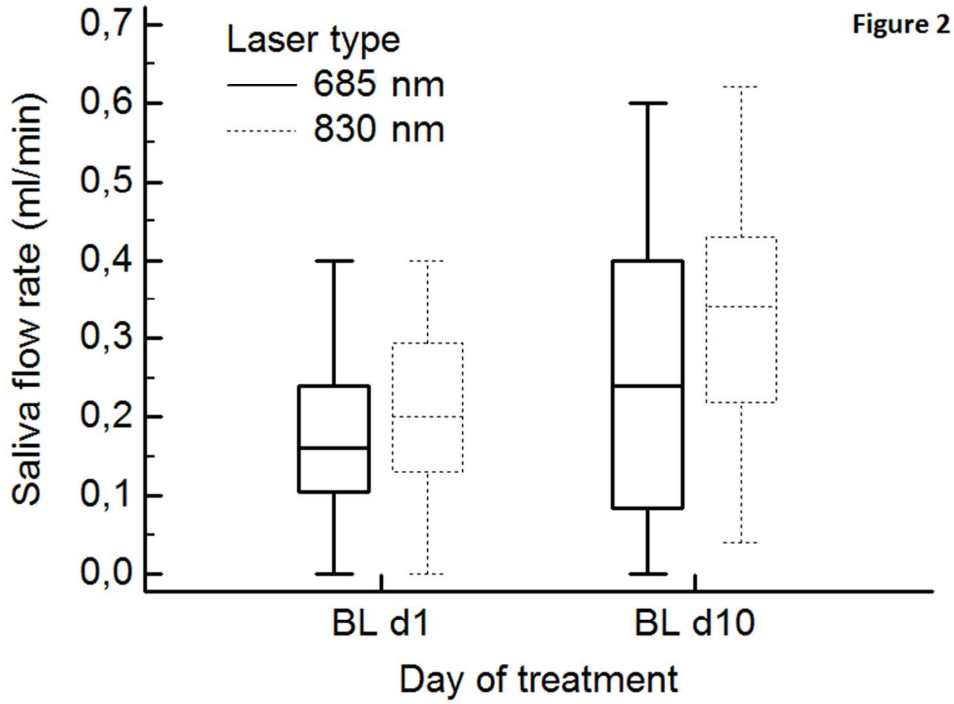

Figure 2. The difference in measured whole unstimulated saliva flow rate (BL-before the laser treatment) on the first and on the last day of the treatment. BL d1= unstimulated saliva flow rate at the first day of treatment, before laser treatment; BL d10= unstimulated saliva flow rate before laser treatment on the 10th day of treatment (T-test for paired examples, $p = 0.0044$ (685 nm), $p = 0.0019$ (830 nm), $p<0.0001$ (all patients)).

211x159mm (96 x 96 DPI)

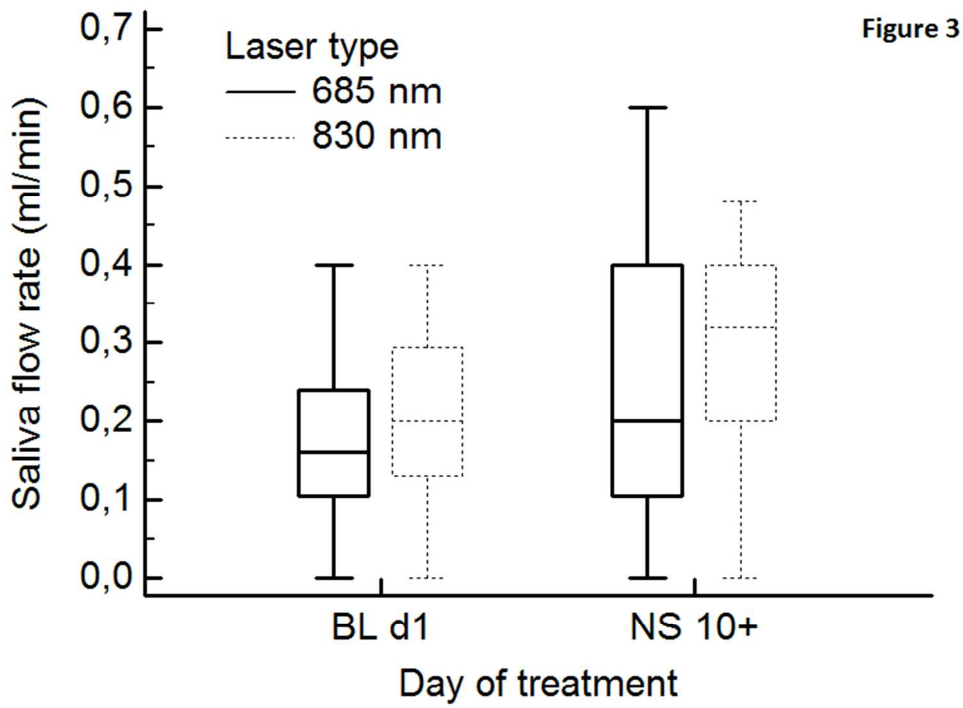

Figure 3. The difference in measured whole unstimulated saliva flow rate before the laser treatment on the first day of the treatment (BL d1) and ten days after the end of the treatment. BL d1=salivary flow rate before laser therapy on the first day; NS 10+= salivary flow rate 10 days after the completion of the laser therapy (T-test for paired examples, $p = 0.0121$ (685 nm), $p = 0.0347$ (830 nm) and all patients ($p=0.0009$)).

211x159mm (96 x 96 DPI)

Figure legends

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Contact information for authors

1. Božana Lončar Brzak, DMD, PhD

Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Gundulićeva 5, 10000 Zagreb, Croatia

Phone: +38514802215

e-mail: loncar@sfzg.hr

2. Livia Cigić, DMD, PhD

Department of Oral Medicine and Periodontology, School of Medicine, University of Split, Šoltanska 2, 21000 Split, Croatia

Phone: +38521557476

e-mail: liviacigic@yahoo.com

3. Marinka Baričević, DMD, PhD

Health Care Centre Zagreb West, Hrvoja Macanovića 2a, 10000 Zagreb, Croatia

Phone: +385915326966

e-mail: baricevicmarinka@gmail.com

4. Ivan Sabol, PhD

Department of Molecular Medicine, Rudjer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia

Phone: +38514561110

e-mail: ivan.sabol@irb.hr

5. Marinka Mravak-Stipetić, DMD, PhD

Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Gundulićeva 5, 10000 Zagreb, Croatia

Phone: +38514802114

e-mail: mravak@sfzg.hr

6. Dubravko Risović, PhD

Molecular Physics Laboratory, Ruđer Bošković Institute, and Centre of Excellence for Advanced Materials and Sensing Devices, Bijenička 54, 10000 Zagreb, Croatia

Phone: +38514561122

e-mail: drisovic@irb.hr