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Successful reduction of SARS-CoV-2 Viral Load by Photodynamic Therapy(PDT) Verified by QPCR, A Novel Approach in Treating Patients in Early Infection Stages

Hans Michael Weber, Yasaman Zandi Mehran, Armin Orthaber, Hadi Hosseini Saadat, Robert Weber, Matthias Wojcik

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Table of Contents

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Abstract

Background: The current COVID-19 pandemic is affecting the life of many people worldwide and although the search and application of vaccines have made fast progress, there are currently only few medications available for risk patients or advanced stages of the disease. Although the predominant Omikron mutation seems to be more harmless we don't know today which new mutations will emerge in the future.

Objective: The objective of this study was to explore if antiviral photodynamic therapy using Riboflavin (Vitamin B2) as photosensitizer in combination with blue and ultaviolet -A light for stimulation could be effective in early stages of the disease for quick reduction of viral load and to prevent the transition of the infection into advanced stages.

Methods: This paper explores a new treatment system with a laser/LED treatment device combined with blue and UVA light therapy. This interventional, non-randomised study involved 140 subjects. Participants were allocated to receive either PDT plus daily testing for 5 days or to receive conventional care plus testing. The viral load and clinical symptoms were measured at the start of the study and after 24, 48, 72, 96, 120 and 168 hours

Results: There was a difference of 6.68 threshold cycles in the mean viral load, with a confidence interval of [5.2; 8.17]. Welch's t-test for two samples indicated this difference was significant ($p < 0.01$). The same test showed that the difference in the means of the control group was not significant.

Conclusions: PDT decreases viral load in patients in early stages of COVID-19. Clinical Trial: ISRCTN10839729 https://doi.org/10.1186/ISRCTN10839729

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Reduction of SARS-CoV-2 Viral Load by Photodynamic Therapy (PDT) Verified by QPCR – A Novel Approach to Treat Patients in Early Infection Stages

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Abstract

Background: The current COVID-19 pandemic is affecting the life of many people worldwide, and although the search for vaccines has made fast progress, there are currently only a few effective medications available. This article explores the usage of blue and ultraviolet A light in combination with riboflavin (vitamin B2), which is known to be one of the best photosensitisers for antiviral photodynamic therapy (PDT).

Methods: This paper explores a new treatment system with a laser/LED treatment device combined with blue and UVA light therapy. This interventional, non-randomised study involved 140 subjects. Participants were allocated to receive either PDT plus daily testing for 5 days or to receive conventional care plus testing. The viral load in the oral and nasal surface and clinical symptoms were measured at the start of the study and after 24, 48, 72, 96, 120 and 168 hours.

Results: There was a difference of 6.68 threshold cycles in the mean viral load, with a confidence interval of [5.2; 8.17]. Welch's t-test for two samples indicated this difference was significant ($p < 0.01$). The same test showed that the difference in the means of the control group was not significant.

Conclusions: PDT decreases viral load in patients in early stages of COVID-19.

Introduction

Photodynamic therapy (PDT) is a promising approach to treat various types of cancer [1–3] and infectious diseases [4]. Unlike traditional methods, PDT is usually not known to cause serious side effects. PDT can also attack and destroy bacteria, viruses and other types of microbes (Fig. 1) [5]. Riboflavin, also known as vitamin B2, is found in food and is used regularly as a dietary supplement. It is needed by the body for cellular respiration. It can be given orally or by injection and is usually very well tolerated, including during pregnancy. There is no evidence of riboflavin toxicity in humans – even when taking high doses over a long period of time, no short-term side effects have been reported [6,7]. However, studies have shown that no more than 25–50 mg of riboflavin can be absorbed per single dose [8]. Of note, pure riboflavin may be replaced with riboflavin-5-phosphate, which has much better water solubility and is the active form of riboflavin.

Riboflavin is used for the photodynamic inactivation of viruses, as it binds to

the nucleic acid bases of the viral RNA. The absorption spectrum of Riboflavin is illustrated in Fig2. When exposed to blue light (447 nm) and ultraviolet A (UVA) light (375 nm), riboflavin oxidises the guanine bases through a single electron transfer reaction. Subsequent reactions produce ½ O_2, hydrogen peroxide and hydroxyl radicals. This leads to irreversible single-stranded breaks in nucleic acids and damage to the pathogens. Riboflavin has been reported to be effective against both enveloped and a number of non-enveloped viruses – including HIV, West Nile virus, Vesicular stomatitis Indiana virus (VSV), Influenza-A-virus (IAV), porcine parvovirus, pseudorabies virus, human hepatitis A virus (HAV), Encephalomyocarditis virus, Sindbis virus and the Middle East Resiratory Syndrom (MERS coronavirus) [9]. A new study published in the United States in April 2020 demonstrated that the COVID-19 virus in plasma products can be eliminated in a short time below the detection limit by using riboflavin and UV light [10]. Another great benefit is that riboflavin also interacts with blue light and UVA light, both of which – especially the latter – exert inhibitory effects on viruses and microorganisms and are safe for clinical usage (Fig. 3) [11,12]. Another option for antiviral PDT would be methylene blue as a photosensitiser. A new study from April 2020 reported that oral methylene blue application in combination with local red light irradiation had good efficacy in reducing the COVID-19 viral load in the respiratory tract [13]. However, compared with riboflavin, methylene blue is not a natural substance, is not as well absorbed in the intestine and has more potential side effects.

COVID-19 is a condition caused by Severe acute respiratory syndrome corona virus (SARS-CoV-2), a virus that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people are asymptomatic but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough, among other symptoms. This can develop into pneumonia.

After a temporary slowdown in summer 2020, COVID-19 infection numbers and death rates have been increasing again in recent months, leading to various restrictions of social and economic life in many countries. The latest developments of new vaccines seem to be promising. However, large-scale production and worldwide distribution logistics take time while questions such as the longevity of immune protection and long-term side-effects, among others, remain unclear. Furthermore, vaccination is a preventive approach and not a treatment for acutely infected patients. Treatments are still needed to help people with COVID-19. The aim of this study was to evaluate whether PDT with riboflavin and a specially designed light treatment kit could fill this treatment gap by helping people in the early stages of infection. This may lead to relief for hospitals and intensive care stations.

We started the investigation in an urgent situation with exploding infections in Gandhi Hospital, Teheran, Iran. We conducted a pilot investigation first with 40 patients [14] and extended the study with another 100 patients to validate our findings. Hence, this paper includes the data from all 140 patients. We obtained retrospective bioethical approval after termination of the study and registered the study retrospectively.

Materials and methods

Study design

This interventional, non-randomised study was conducted between October 2020 and February 2021 at Gandhi Hospital in Tehran, Iran. All subjects in the study were in the early stages of COVID-19: they had received a positive quantitative polymerase chain reaction (QPCR) test result and most were already showing typical symptoms such as sore throat, fever, cough and often a loss of smell and taste. Nobody had experienced lung infection or required oxygen therapy; therefore, chest computed tomography was not done at this time. The participants were allocated randomly to receive either PDT plus daily testing for 5 days or to receive conventional care plus testing. The viral load was measured at the start of the study and after 24, 48, 72, 96, 120 and 168 hours. The exclusion criteria were: (1) late infection stages with oxygen therapy, (2) pregnancy and (3) children aged under 10 years of age.

The study employed a two-armed, repeated measures design. The primary outcome was viral load, measured using the QPCR threshold cycle (CT) value at baseline and after 24, 48, 72, 96, 120 and 168 hours. The focus of the analysis was the difference in the CT values (‘CT_ and CTday’) in two groups: the treatment group (‘PDT’) and subjects that received standard care (‘Std’). In this study, the CT values ranged from 15.4 to 40. CT_1 denotes the variable with the measurements on the first day of the trial. The secondary outcomes were clinical symptoms measured by using a visual analogue scale (VAS) at baseline and 24, 48, 72, 96, 120 and 168 hours. The recorded symptoms included headache, breathing problems/chest pain and painful coughs (headache, breathing chest, cough), denoted in the same fashion. The symptoms were rated on a nominal scaled, with ‘1’ if the VAS score was higher than 4, and ‘0’ otherwise. Possible confounders that were checked include age (‘AGE), measured in years, and gender (‘Gender’), coded as ‘1’ for female and ‘0’ for male. We did not include a third arm to measure the effects of UVA light without riboflavin as a photosensitiser because Darnel et al. [15] showed that UVA exposure alone did not exert effects on virus inactivation over a 15-minute period.

Equipment

The equipment used in this study is manufactured by Weber Medical GmbH (Lauenfoerde, Germany). It comprised a Weber Medical Spectra laser/LED watch with four red diodes (658 nm, 5 mW each), two green diodes (532 nm, 5 mW each), two blue diodes (447 nm, 5 mW each) and two yellow diodes (589 nm, 5 mW each) (Fig. 4).

A special nose adapter can be attached to the watch with two LEDs (one with blue light at 447 nm, 5 mW, and one with UVA light at 375 nm, 5 mW). In addition, there is a mouth adapter with 24 LEDs (12 with blue light at 447 nm, 5 mW each, and 12 with UVA light at 375 nm, 5 mW each) (Fig. 5).

Capsules containing 100 mg of highly pure riboflavin-5-phosphate each were

obtained from Ultra Botancia LLC (Oklahoma City, OK, USA). The US supplier for this batch was a US based company called PureBulk Inc., (Roseburg, USA). Other supplies included one spray bottle with a mouth and nose applicator and one UVC sterilisation box.

Intervention

Patients were assigned to two groups based on the sequence of hospital admission; each group comprised 70 patients. The treatment group received daily PDT and testing for 5 days and the control group received conventional care plus testing for 5 days. Conventional treatment comprised Remdesivir 100 mg daily for 5 days, Vitamin C orally 1000 mg daily, Hydroxychloroquine 200 mg daily for 10 days, Famotidine 40 mg every 12 hours, Ceftriaxone 1 g every 12 hours, and Atorvastatin 40 mg daily for 10 days.

All patients had a positive COVID-19 test result at the beginning of the study. They were in an early infection stage with mild symptoms like fever, dry cough, headache, breathing difficulties, fatigue, etc. QPCR was performed on days 1, 2, 3, 4, 5 and 7 in both groups.

The treatment protocol for the experimental group appears below. It was carried out for 5 days.

1. One capsule with 100 mg riboflavin-5-phosphate was taken with a meal for systemic application.

2. A second capsule of riboflavin-5-phosphate (100 mg) was dissolved in 200 ml of water in a glass (for local application in the nose, mouth and throat).

3. After 1 hour, the light treatment device (Spectra Watch) was fixed on the wrist and switched on for 60 minutes (for additional systemic effects) (Fig. 4).

4. After 15 minutes, the spray bottle was filled with some of the dissolved riboflavin solution and sprayed three times into both nostrils.

5. The mouth was flushed three times with the rest of solution in the glass with gargling (ideally, the remaining solution was drunk).

6. After 15 minutes, the nose and mouth applicators were attached to the laser watch. Each nostril was treated for 10 minutes with blue and UVA light (switch sides after 10 minutes) and the inside the mouth and throat were treated for 20 minutes (Fig. 5).

The total energy applied to the mouth and throat was 144 J over 20 minutes and the total energy applied to the nose area was 12 J over 20 minutes. The energy per square centimetre is difficult to determine because the surface area of the mouth/throat and nose is difficult to calculate and the LEDs do not have direct

contact with the mucosa. The LEDs of the mouth adapter were located on the top, back, sides and front of the adapter, so irradiation was delivered all over the oral and nasal cavity.

The wrist arteries were irradiated with a Spectra laser/LED watch described in the 'Equipment' section. The applied energy was 18 J per point over 60 minutes, for total energy of 180 J. Irradiation of the wrist arteries works as indirect, non-invasive blood irradiation (Fig. 4) [16] in which red light stimulates the immune system [17,18], green light improves the rheological properties of the blood [19], blue light has an antimicrobial effect and improves the release of nitric oxide (NO) from the haemoglobin–NO complex [20,21] and yellow light stimulates vitamin D3 production, which has anti-inflammatory effects [22,23]. Besides, the Spectra watch serves as energy source for the adapters used for the mouth/throat and nose.

If not otherwise stated, all mentions of statistical significance refer to an alpha level of 5%. Computations were performed in the R programming language.

Results

In total, 78 female and 62 male subjects participated in the study. Based on chi-square tests, there were no difference in gender between the treatment and control groups. In the control group, 57.1% of the subjects (40) were female and 42.9% of the subjects (30) were male, while in the treatment group 54.3% (38) were female and 45.7% (32) were male. The mean age was 42.8 (standard deviation [SD] 14.99) years in the treatment group and 44.9 (SD 14.65) years in the control group (Fig. 6). Based on t-tests, there were no differences in the baseline characteristics between the groups. Further analysis, however, showed a significant difference between the treatment and control group in the mean CT value and symptoms after 5 days, when controlled for the differences at the beginning. Table 1 presents the p values for differences in symptoms, distinguished between gender and treatment groups.

The first hypothesis tested (H1a) is patients in the treatment group show significant improvement in clinical symptoms and viral load assessment after 5 days of PDT treatment. The mean CT value in the treatment group was 29.63 at day 1 and 36.3 at day 5, for a difference of 6.68 threshold cycles and a confidence interval of [5.2; 8.72]. Based on Welch's t-test for two samples, this difference was significant ($p < 0.01$). The same test showed no difference in the means of the control group.

To further explore the difference between the treatment and control groups, and considering that the treatment group had a higher mean CT value on day 1 compared with the control group, we tested a second hypothesis (H1b): CT values in the treatment group increase (denoting improvement) significantly compared with the control group.

For a joint analysis of the treatment and time effects from day 1 to 5, a

longitudinal mixed model was established comprising treatment time and gender plus all interactions as fixed effects and subject as random effect. A linear mixed model revealed 4 extreme outliers in the residual plot which were subsequently removed without affecting the outcome notably. To control for all interactions, a linear mixed model was constructed with all interactions of treatment, time, gender and age, allowing random variation across subjects. All fixed effects were found significant, except age and the interaction of time and gender, which were subsequently excluded in the final model. Fig. 7 shows the estimated least squares means of the CT for both genders.

Overall, the treatment group had higher CT values; this difference was more distinct in the female participants. While there was no clear difference between the treatment and control groups regarding the CT values on day 1 for the males, the female subjects in the treatment group already had higher values. Note that in these results, six subjects of the treatment group with no viral load (‘negative’) have been excluded, as well as two subjects of the control group, who had to be transferred to an intensive care unit.

Discussion

After correcting for possible confounders, the subjects in the treatment group had significantly higher CT values, indicating a lower viral load (Fig. 8) Male participants in the treatment group showed fewer symptoms compared with male participants in the control group. For female participants, breathing problems and painful cough were reduced significantly in the treatment compared with the control group.

The light used in *in vitro* studies for riboflavin stimulation was generated with UV lamps that deliver a wide portion of the electromagnetic, spectrum including UVC, UVB and UVA light. UVC light ranges from 100 to 280 nm, UVB ranges from 280 to 315 and UVA range from 315 to 400 nm. Because UVC and UVB light damage white blood cells and can even cause cancer, only UVA light can be used safely to treat human subjects. The maximum absorption and stimulation of riboflavin is between 375 and 447 nm. In a study published in August 2020, Rezaie et al. [11] could not determine relevant risk for the clinical use of UVA light in humans. The light system used in this treatment was equipped with several LEDs with a narrow-band UVA wavelength of 370 nm and a blue wavelength of 447 nm. These wavelengths can be regarded as safe.

The treatment presented in this study is recommended in early cases – only in stages 1 and 2 – as which time the treatment can be carried out by the patient at home for post-contact prevention or while in quarantine. The precise aim of the treatment is symptom reduction, reduced hospitalisation and prevention of complications. It should be used to reduce symptoms and to avoid hospitalisation of patients with artificial respiration with all possible late complications. Our aim was to find a way to prevent severe illness in general, not to evaluate the effect of this treatment on the lungs of patients in the advanced stages of COVID-19. We wanted to treat early infections with no or mild beginning symptoms before the lungs become affected and prevent this

complication. We cannot conclude whether this treatment would benefit patients with affected lungs. This should be investigated in an invasive study with intravenous riboflavin administration and perhaps direct lung irradiation via bronchoscopy with cylindrically irradiating fibre optics.

Our study supports the hypothesis discussed by Tariq et al. [12]: PDT is one of the safest antiviral therapy. Indeed, we recorded no side effects during the duration of this trial.

Limitations

The mean age of the participants was 43.9 years, which is relatively low given that the most severe courses of COVID-19 usually occur in older individuals. Hence, further investigation of the effectiveness of this treatment in older patients is required. On day 1, the mean CT value in the treatment group was significantly higher than that of the control group. This difference could suggest some performance bias because the subjects were already receiving treatment, which could not be concealed and constituted extra care.

Conclusion

In the early phases of COVID-19, PDT with riboflavin as a photosensitiser seems to decrease the viral load in mouth and nose and improves the patient's outcomes. Besides increasing the qPCR values in the swab tests from mouth and nose the therapy leads to an impressive improvement of clinical symptoms and patients condition.

Figure legends

Fig. 1. The principles of photodynamic therapy.
Fig. 2. The absorption spectrum of riboflavin-5-phosphate.

Fig. 3. The mechanism of antiviral photodynamic therapy.
Fig. 4. The laser/LED watch with red, green, blue and yellow LEDs (5 mW each).
Fig. 5. The treatment kit containing a laser/LED watch with oral and nasal adapters and application on a patient.
Fig. 6. Schema of study design

Fig. 7. CT results based on 71 female and 61 male subjects. Note: Higher CT-values indicate a lower viral load; Std-standard therapy, PDT-photodynamic therapy

Fig. 8. Development of CT values within 5 days of verum group (PDT) in comparison to control group (Std)

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Fig. 1

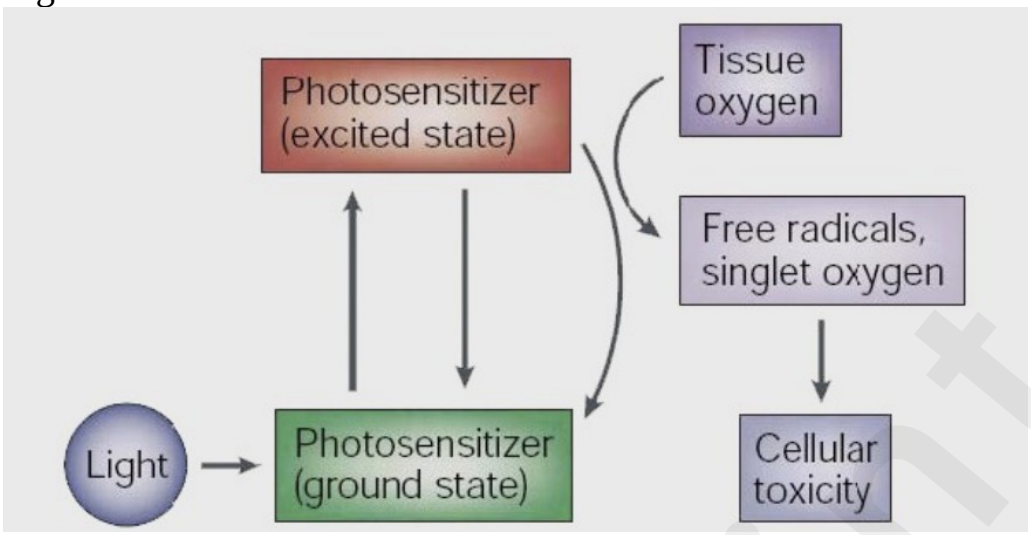

Fig. 2

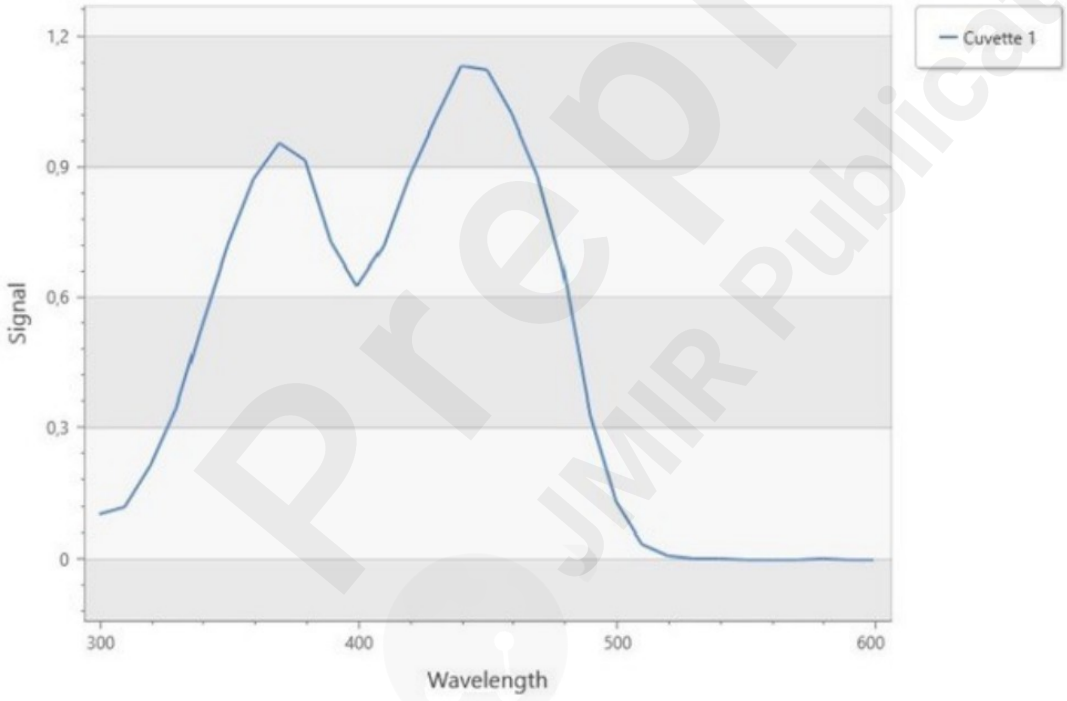

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Fig. 3

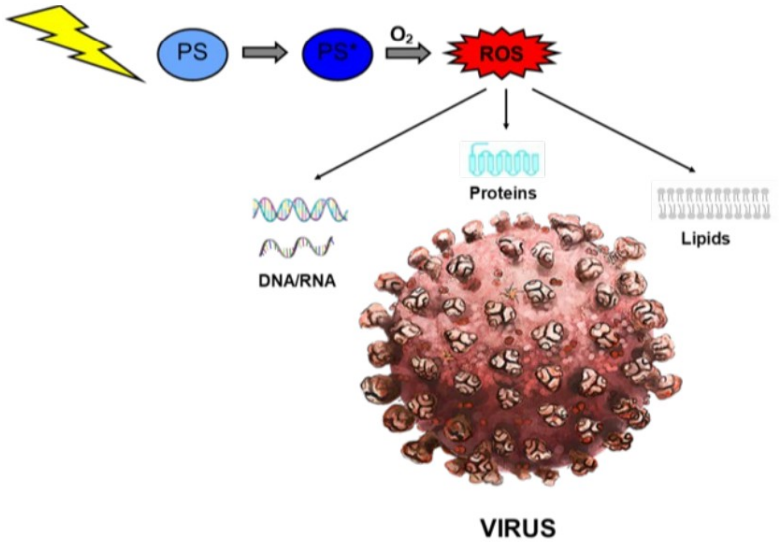
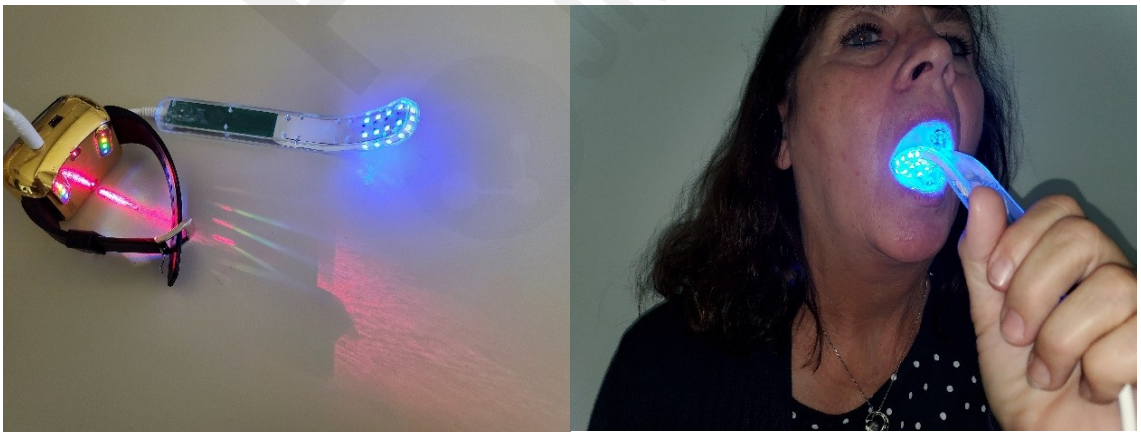


Fig. 4

Fig.5



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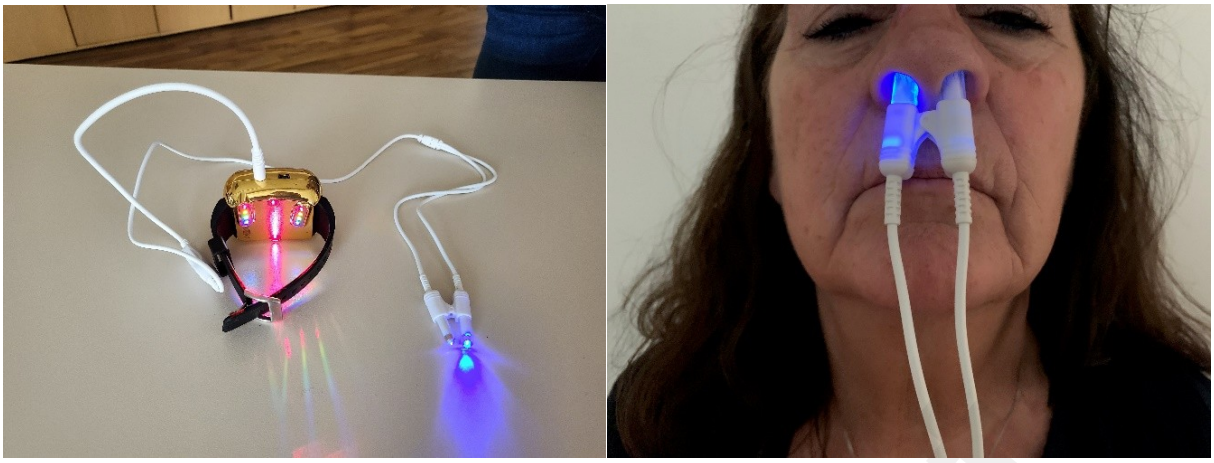

Fig. 6

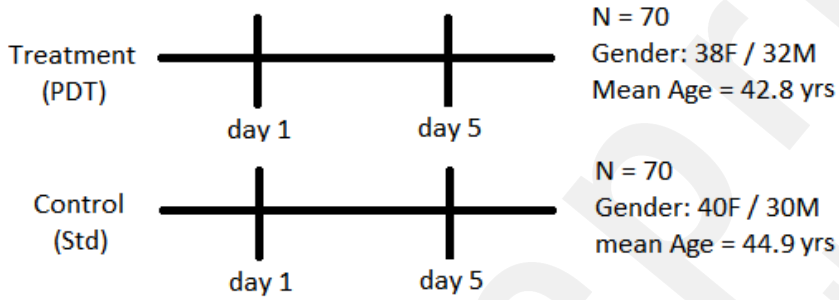

Fig. 7

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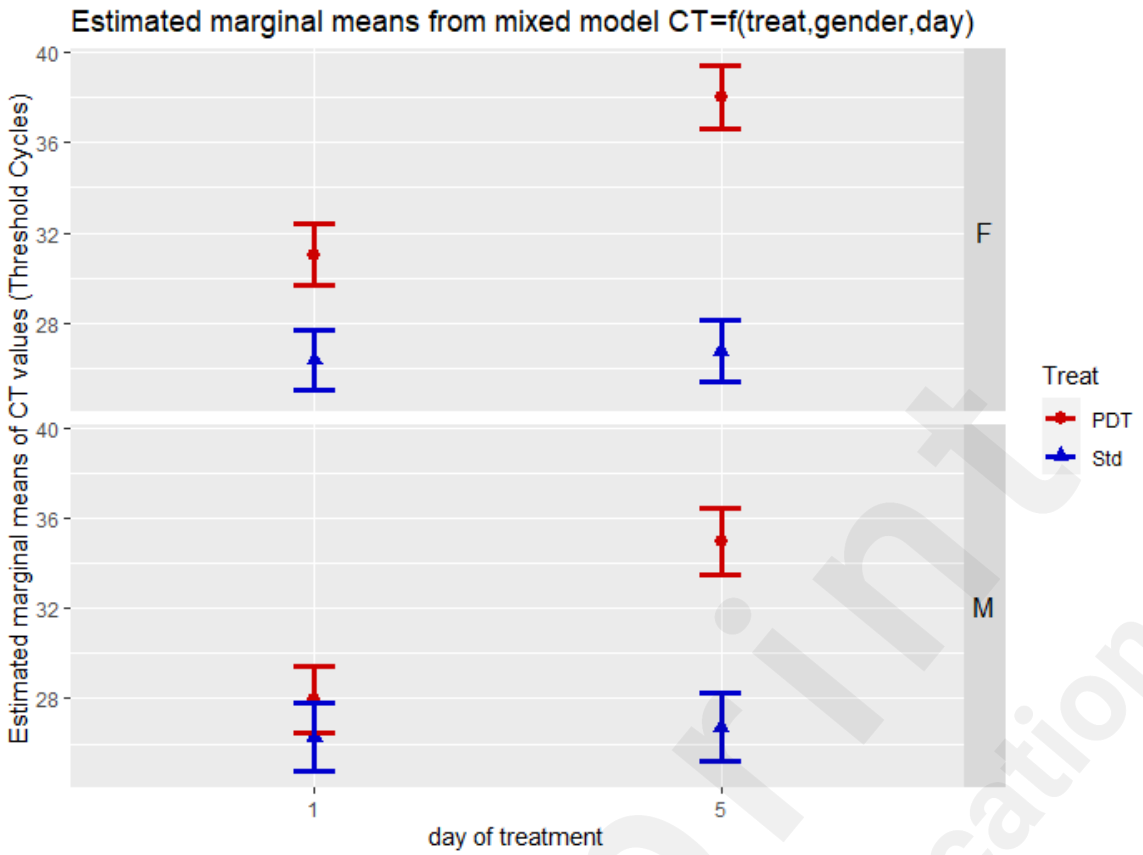

Fig. 8.

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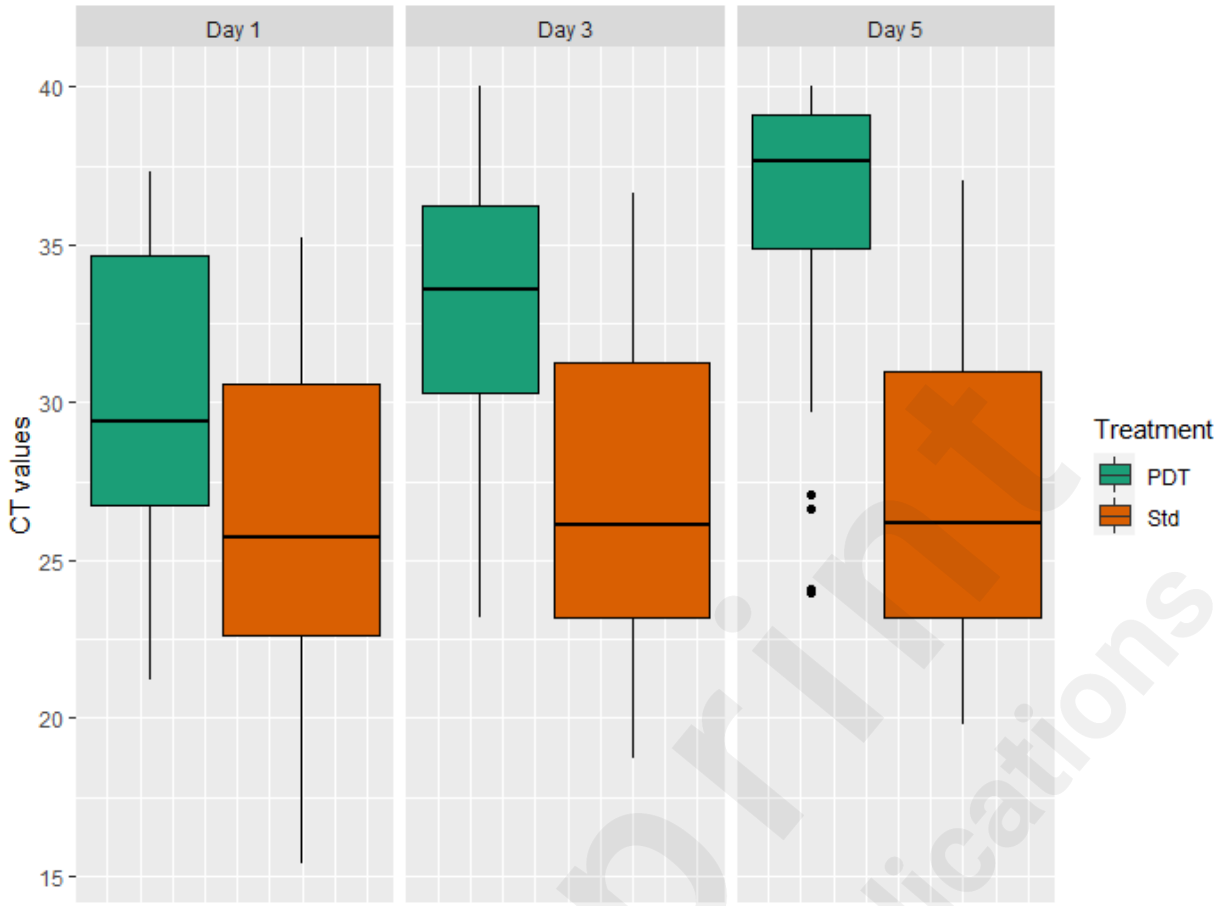

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Tables

Table 1 Symptom frequencies.

Symptom	Day	Gender	PDT (%)	Std (%)	p	Statistical significance
Coughing	1	M	84.38	66.67	0.141	
	5	M	15.63	63.33	<0.001	***
	1	F	73.68	80.00	0.595	
	5	F	10.53	62.50	<0.001	***
Breathing difficulties	1	M	71.88	80.00	0.558	
	5	M	34.38	73.33	0.003	***
	1	F	89.47	67.50	0.027	*
	5	F	28.95	57.50	0.013	*
Headache	1	M	59.38	73.33	0.291	
	5	M	12.50	56.67	<0.001	***
	1	F	65.79	52.50	0.258	
	5	F	28.95	37.5	0.477	
Fever	1	M	46.88	80	0.033	*
	5	M	0	20	0.009	**
	1	F	55.26	32.5	0.067	
	5	F	0	27.5	<0.001	***

Based on 78 female (F) and 62 male (M) subjects. PDT, photodynamic therapy; Std, standard therapy. The asterisks indicate statistical significance between the PDT and Std groups on days 1 and 5: *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

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Competing interests: Hans Michael Weber has filed a now-pending patent on the device that was used in the study. Robert Weber is leader of the ISLA Research group. All other authors declare no competing interests.

Data and materials availability: Raw data can be released upon reasonable request to the corresponding author.

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