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Case Report

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Photodynamic therapy (pdt) in early stages of acute adult covid-19 patients: effects on viral load measured by qpcr

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Abstract

Background: *The Covid-19 pandemic has negatively impacted Global Health and the world's economy dramatically since early 2020. Although the development of vaccines has made fast progress, there are currently only a few effective medications and treatment options available for infected patients available.*

Objectives: *The objective of this study was to evaluate the efficacy and safety of Photodynamic Therapy (PDT) with Riboflavin and a specially designed light treatment kit with blue and UVA light as a treatment tool for reducing viral load and clinical symptoms in patients with early stage Covid-19 infection.*

Methods: *This interventional, non-randomized study involved 140 adult 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 cavity and clinical symptoms were measured at the start of the study and after 24,48,72,96,120 and 168 hours.*

Results: *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. Further analysis showed a significant difference between the treatment and control group in the clinical symptoms after 5 days as well, when controlled for the differences at the beginning.*

Conclusion: *PDT decreases viral load and improves clinical symptoms in patients in early stages of Covid-19 significantly. It could be a promising tool for treatment of acutely infected patients in early stages to prevent progression of disease.*

Keywords: Global Health, Covid-19, Conventional Care, Skin, Photosensitizer, Absorption Spectrum

Introduction

Photodynamic therapy (PDT) is a promising approach in the treatment of various types of cancer [1-3] and infectious diseases [4]. The principle is the stimulation of a light sensitive drug (photosensitizer) which is applied either on the skin as a cream, applied orally or injected into the blood circulation. In cancer treatment the photosensitizer is integrated into tumor tissue by endocytosis and is subsequently irradiated with light of specific wavelength that matches the absorption spectrum of the photosensitizer. This light activation process induces various chemical processes such as the development of radical oxygen species that ultimately lead to the destruction of tumor tissue or microbes and viruses.

In opposition to conventional treatment methods, PDT has a high safety profile and is not known to have serious adverse effects. PDT has antimicrobial properties and it is a viable option for safe eradication of bacteria, viruses and other types

of microbes (Figure 1) [5]. Riboflavin, commonly known as vitamin B2, is found in food and is used regularly as a dietary supplement. Riboflavin is an essential nutrient required by the body for cellular respiration and several critical functions. It can be administered orally or by injection and is well tolerated, including during pregnancy. Riboflavin is water soluble, and there is no evidence of riboflavin toxicity in humans. It has been shown to be safe with no short term side effects reported when taking high doses over a long period of time [6,7]. Studies show that maximum absorption of riboflavin from oral delivery is 20-50mg. To increase the bioavailability, pure riboflavin can be replaced with the active form, riboflavin-5-phosphate which has a higher solubility in water.

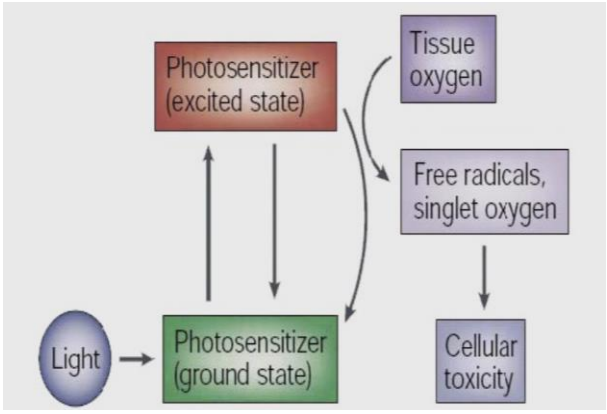

Figure 1: The principles of photodynamic therapy.

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 Figure 2. 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 ½O2, hydrogen peroxide and hydroxyl radicals.This leads to irreversible single-stranded breaks in nucleic acids and damage to the pathogens. Riboflavin-PDT 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 Respiratory Syndrome (MERS coronavirus) [9]. A study published in the United States in April 2020 demonstrated that the COVID-19 virus in plasma products can be eliminated below the detection limit rapidly by using riboflavin in conjunction with UV light [10]. Additionally, riboflavin interacts with UVA light and blue light, both of which-especially the former-exert inhibitory effects on viruses and microorganisms and are safe for clinical usage (Figure 3) [11,12]. Another option for antiviral PDT would be methylene blue as opposed to riboflavin as a photosensitizer. A study from April 2020 reported that oral methylene blue application in combination with local red light irradiation was efficacious in reducing the COVID-19 viral load in the respiratory tract [13]. However, unlike riboflavin, methylene blue is not a natural substance, is not as well absorbed in the intestine and has more potential side effects.

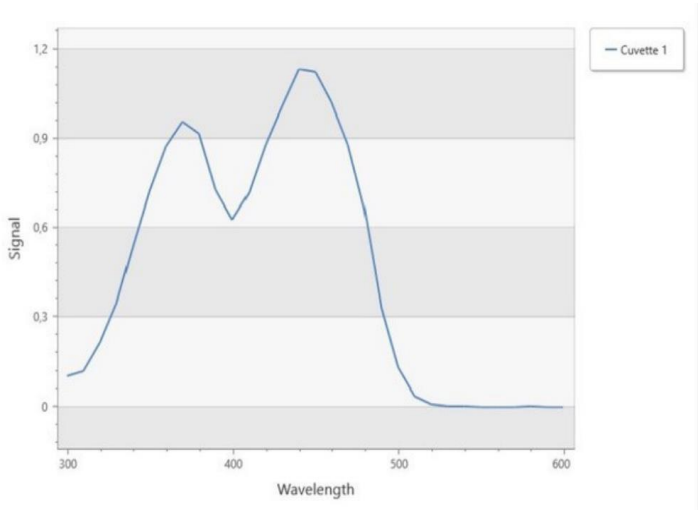

Figure 2: The absorption spectrum of riboflavin-5-phosphate.

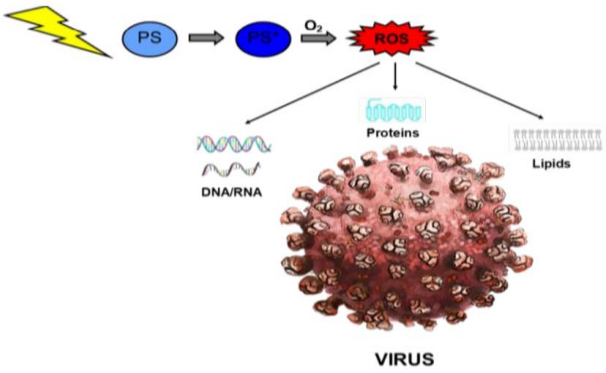

Figure 3: The mechanism of antiviral photodynamic therapy.

COVID-19 is a condition caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), a virus that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Many people present asymptomatically 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.

Different vaccinations are available now. However, vaccination is a preventive approach and not a treatment for acutely infected patients. Treatments are still needed to help people with active 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 and help people in the early stages of infection. This may provide relief for hospitals and reduce the burden seen in intensive care units.This investigation started in an urgent situation with extremely high Covid-19 infection numbers in Iran. The pilot investigation was first conducted with 40 patients [14] and was extended with another 100 patients to validate the findings. This paper includes the data from all 140 patients.

Materials and Methods

Study design

This interventional, non-randomized 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. No participants had experienced lung infection or required oxygen therapy; therefore, chest computed tomography was not done at this time. The participants were randomly allocated to receive the PDT therapy 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) patients aged under18 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 the 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 and denotes the variable with the measurements on the first day of the trial. Secondary outcomes were clinical symptoms measured by using a visual analogue scale (VAS) at baseline, 24,48,72,96,120 and 168 hours. The recorded symptoms included fever, 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 confounding variables that were accounted for included 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 photosensitizers 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 included 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) (Figure 4).

A special nasal 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 oral 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) (Figure 5).

Capsules containing 100 mg of highly pure bioactive riboflavin-5-phosphate 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.

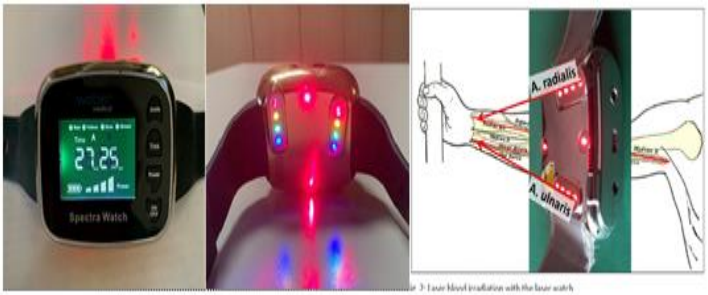

Figure 4: The laser/LED watch with red, green, blue and yellow LEDs (5 mW each).

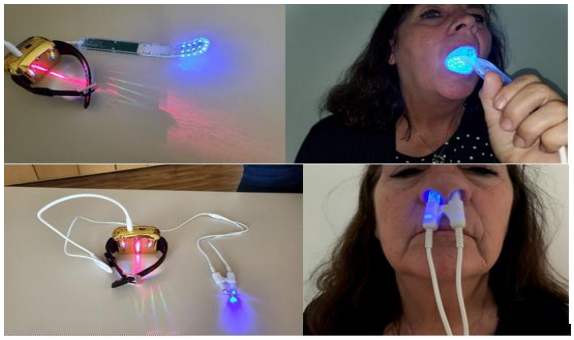

Figure 5: The treatment kit containing a laser/LED watch with oral and nasal adapters and application on a patient.

Intervention

Patients were assigned to two groups based on the sequence of hospital admission; both groups had 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 included Remdesivir 100 mg daily for 5 days, 1000 mg oral Vitamin C 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 such as fever, dry cough, headache, breathing difficulties, fatigue. QPCR was performed on days 1,2,3,4,5 and 7 in both groups.

The treatment protocol, which was adminstered for a duration of 5 days for the experimenta l group appears below:

1. One capsule with 100 mg riboflavin-5-phosphate was taken with a meal for systemic delivery.
2. A second capsule of riboflavin-5-phosphate (100 mg) was dissolved in 200 ml of water (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) (Figure 4).
4. After 15 minutes, the spray bottle was filled with the dissolved riboflavin solution and sprayed three times into both nostrils.
5. The mouth was flushed three times with the rest of the solution and gargled (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 (switching sides after 10 minutes) and the inside the mouth and throat were treated for 20 minutes with the oral applicator (Figure 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 in the mouth applicator are located on the top, back, sides and front of the applicator, allowing irradiation to cover the entirety of the nasal and oral cavity.

The wrist arteries were irradiated with the Spectra laser/LED watch described in the 'Equipment' section. The applied energy was 18 J per point over 60 minutes, for a total energy of 180 J. Irradiation of the wrist arteries works as indirect, non-invasive blood irradiation (Figure 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]. Additionally, the primary purpose of the Spectra Watch is to serve as the energy source for the oral and nasal adaptors.

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

Safety

The light used in in vitro studies for stimulation of riboflavin was generated with UV lamps that deliver a wide range of the electromagnetic, spectrum including UVC, UVB and UVA light. UVC light ranges from 100nm to 280 nm, UVB ranges from 280nm to 315nm and UVA range from 315nm to 400 nm. Because UVC and UVB light damage white blood cells and are correlated to onset of 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.

Ethical Considerations

The study had been initiated in an urgent situation with extremely high Covid-19 infection numbers in Iran. An effective treatment was needed urgently, and our new concept was presented to the University of Teheran for Institutional Review Board (IRB) approval. We got a verbal approval so that we could start immediately after application, but unfortunately official sessions of the IRB committee did not take place at this time because of the confusing and pressing situation and the rapid increase in COVID-19 infections. After the agreement of the Gandhi Hospital, we started the investigation due to the urgency of the situation. We conducted a pilot investigation with 40 patients [14] and extended the study with another 100 patients to validate our findings. This paper includes the data from all 140 patients. We obtained retrospective bioethical approval after termination of the study and registered the study retrospectively.

Data Availability

Raw data can be released upon reasonable request to the corresponding author.

Results

In total, 78 female and 62 male subjects participated in the study. Based on chi-square tests, there was 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 (Figure 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.

The first hypothesis tested (H1a) is that 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 group, 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 consisting of 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. Figure 7 shows the estimated least squares means of the CT for both genders.

Overall, after correcting those possible confounding variables, the subjects in the treatment group had significantly higher CT values compared to the control group, indicating a lower viral load (Figure 8) after the 5-day treatment intervention. This difference was more distinct in the female participants.

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.

Table 1 presents the p values for differences in symptoms, distinguished between gender and treatment groups. The results indicate statistical significance between the PDT and control group on days 1 and 5 with significant improvements of clinical symptoms (coughing, breathing difficulties, headache, fever) only happening within the PDT group.

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.						

Table 1: Symptom frequencies.

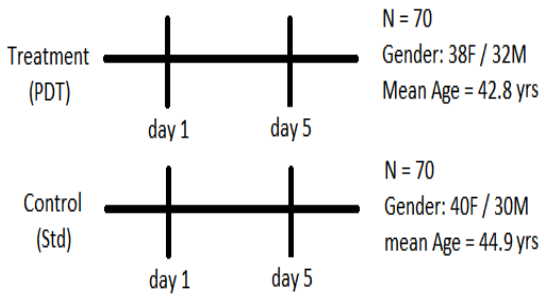

Figure 6: Schema of study design.

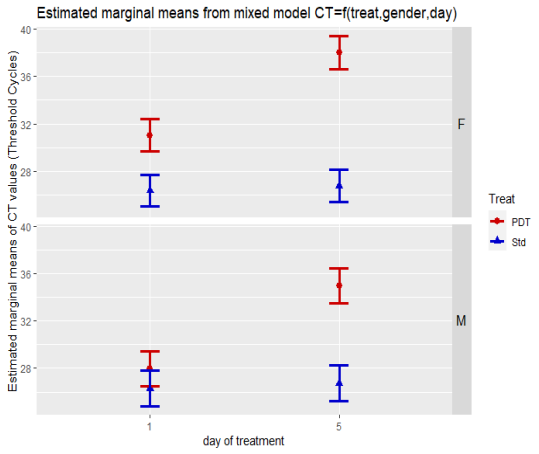

Figure 7: CT results based on 71 female and 61 male subjects. Note: Higher CT-values indicate a lower viral load; Std-standard therapy, PDT-photodynamic therapy.

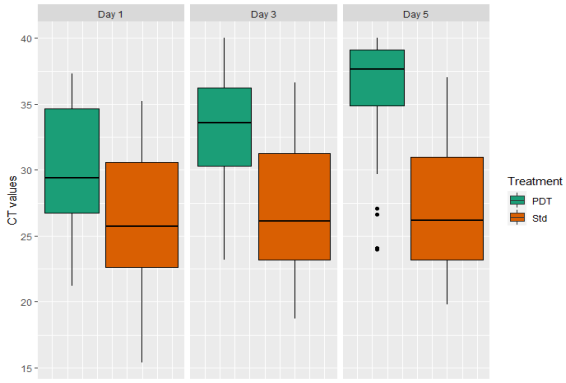

Figure 8: Development of CT values within 5 days of verum group (PDT) in comparison to control group (Std)

Discussion

Despite vaccination being an important preventive approach, there is still a gap in viable therapies for effective treatment of acutely infected patients.

The efficacy of Photodynamic Therapy (PDT) against several viruses including SARS-CoV-2 has been demonstrated in several in-vitro studies over the last couple of years. Our presented study is the first in-vivo approach of using PDT with the photosensitizing agent, riboflavin and a specially designed treatment kit against SARS-CoV-2.

The results indicate that PDT plus riboflavin is efficacious in improving clinical symptoms and reducing viral load in patients suffering from the early stages of Covid-19. While no significant improvements with conventional care could be observed in the control group, there was a significant improvement of clinical symptoms such as coughing, breathing difficulties, headache and fever in the PDT group.

Comparison of viral load assessment by QPCR showed significant reduction in the PDT group, compared to no statistical difference in the control group. Additionally, it is important to emphasisethat PDT led to no side-effects at all; this is in accordance with all the in-vitro and safety data for Riboflavin-based Photodynamic Therapy. The hypothesis discussed by Tariq et al. [12] could be supported: PDT is one of the safest antiviral therapies.

Another advantage of PDT is the simple and cost effective application which can be done even at home by the patient in early disease stages. This could not only relieve the hospitals with their intensive care units but also prevent excessive expenses for health insurances and damage to the global economy (due to economic and social lockdowns).

The treatment presented in this study is recommended in early stages of disease-when 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. 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. The objective was to treat early infections that presented with no symptoms or mild, beginning stage symptoms before the lungs became impacted in an effort to prevent this complication. We cannot conclude whether this treatment would benefit patients with progressed disease to the lungs. This should be investigated in a separate study with direct lung irradiation via bronchoscopy with cylindrically irradiating fiber optics.

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

The presented study shows the first evidence for a successful treatment of Covid-19 patients in early stages of disease through Photodynamic Therapy. The applied protocol with a combination of riboflavin as a photosensitizer with UVA and blue light proved to be effective in reducing the viral load of patients and in improving clinical symptoms significantly.

This therapeutic intervention is suitable for early stages of infection when first clinical symptoms like fever, sore throat or breathing problems arise. Consequently, it is expected to accelerate recovery and prevent patients from progressing into advanced stages.

Photodynamic Therapy might be an important tool in lowering global Covid-19 burden in addition to prevention by vaccination.

Acknowledgment

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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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