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Perspective

Pulsed Ultraviolet C as a Potential Treatment for COVID-19

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ABSTRACT: Currently, low dose radiotherapy (LDRT) is being tested for treating life-threatening pneumonia in COVID-19 patients. Despite the debates over the clinical use of LDRT, some clinical trials have been completed, and most are still ongoing. Ultraviolet C (UVC) irradiation has been proven to be highly efficient in inactivating the coronaviruses, yet is considerably safer than LDRT. This makes UVC an excellent candidate for treating COVID-19 infection, especially in case of severe pneumonia as well as the post COVID-19 pulmonary fibrosis. However, the major challenge in using UVC is its delivery to the lungs, the target organ of COVID-19, due to its low penetrability through biological tissues. We propose to overcome this challenge (i) by using pulsed UVC technologies which dramatically increase the penetrability of UVC through matter, and (ii) by integrating the pulsed UVC technologies into a laser bronchoscope, thus allowing UVC irradiation to reach deeper into the lungs. Although the exact characteristics of such a treatment should yet to be experimentally defined, this approach might be much safer and not less efficient than LDRT.

Keywords: UVC; Coronavirus 2 (SARS-CoV-2); COVID-19; Fibrosis; Optic fibers; Laser bronchoscope

1. Introduction

The ongoing pandemic of Coronavirus Disease 2019 (COVID-19), which is caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), is still considered as a global pandemic. As of 25 January 2023, there have been over 664 million confirmed cases of COVID-19 infections worldwide, with more than 6.7 million fatal outcomes [1]. Despite a 25% decrease in COVID-19 cases, there is a 13% increase in the new reported deaths in the last month [1]. Coronaviruses include a large family of single-stranded, positive-sense RNA viruses, which usually cause influenza-like symptoms that might evolve toward severe acute respiratory distress syndrome with pulmonary inflammation, extensive lung damage and eventually death [2,3]. The pulmonary fibrotic disorders range from fibrosis associated with organizing pneumonia, to severe acute lung injury with various fibrotic changes [4]. Pulmonary fibrosis is a well described manifestation in SARS-CoV-2 infections, both in animal models and in humans [4–9]. More importantly, numerous studies estimate that approximately 70–80% of the people infected with SARS-CoV-2 will continue to suffer from a wide range of post-infection sequelae, with pulmonary fibrosis being one of the more frequent and severe complications [10,11]. The severe health and social implications of the COVID-19 pandemic, and the lack of proper treatment, have stimulated the scientific and medical communities to propose different therapeutic strategies [11]. Since April 2020, several papers have appeared which proposed the clinical use of lung low dose radiotherapy (LDRT) to treat life-threatening pneumonia in COVID-19 patients. These suggestions are based on an earlier review of literature published between 1905 and 1943 on LDRT for viral or bacterial pneumonia [12]. Despite the controversy and debates over this approach, its risks and its efficiency, some clinical trials have been completed, and most are still ongoing [11–16]. The current clinical trials use doses ranging between 0.1 to 1.5 Gy, which are more than 2-orders higher than the yearly dose limit for the general public [17].

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2. UVC Irradiation as a Potential Antiviral Agent

Unlike the X-ray- based LDRT, UVC is electromagnetic radiation with a wavelength within the range of 100–400 nm. It is divided into four distinct spectral areas: vacuum UV (100–200 nm), UVC (200–280 nm), UVB (280–315 nm), and UVA (315–400 nm) [18]. UVC has been known to be highly germicidal for more than a century [18]. It is absorbed by the nucleic acids of a microorganism and induces damage to its genetic material, often as a result from the formation of cyclobutane pyrimidine dimers (CPDs). This dimerization is followed by defective viral/bacterial replication process, or no replication at all [18,19]. It is long known that coronaviruses, much like other viruses and bacteria, are sensitive to UVC [18,19]. This is especially noted within the range of 220–280 nm, known as "the germicidal spectrum", where UVC is strongly absorbed by the nucleic acids of the microorganisms [19]. During the past years, numerous studies have demonstrated that UVC efficiently and safely inactivates SARS-CoV-2, and the idea of using UVC to disinfect surfaces, air, and liquids [20–24] was introduced. However, the therapeutic application of UVC irradiation for the treatment of patients with severe COVID-19 is limited because of two major challenges: (i) UVC irradiation has low penetrability through biological tissues [25]; thus, it is incapable of reaching the lungs, the primary target organ of SARS-COV-2, and inactivates the virus; (ii) some risks have been connected to UVC [26].

3. Possible UVC Application for Therapeutic Treatment for COVID-19 Infection

In order to enable the clinical use of UVC for the treatment of COVID-19, the above challenges must be resolved. To overcome the low penetrability challenge, two major requirements are essential: (i) maximuming proximity between the UVC irradiation source and the target organ, and (ii) using the pulsed UVC technology. There is strong evidence determining that using pulsed UV light instead of continuous UV light can enhance its penetrability [19,27]. Thus, it is only reasonable to assume that pulsed UVC might have greater penetrability compared to continuous UVC. Some indication is implied by the study presented by Do-Kyun & Dong-Hyun (2018) [28]. Hence, we propose to overcome this challenge by applying the novel pulsed UVC technologies by integrating it into laser bronchoscopy, thus presumably allowing UVC irradiation to reach deeper into the lungs, the target organ of SARS-COV-2 (Figure 1). While continuous UVC penetrates only up to 20 μm through the skin, the pulsed UVC have up to 3-order higher penetration capacity through biological tissues, followed by a more efficient germicidal effect [19,25,27,28]. In preliminary calculations, we have found that the penetration depth should be around 0.5 cm (see Suppl. Materials Figure S4)—which should be enough for delivering UVC from the bronchoscope to the lung tissue. Our calculations also show that the pulsed UVC irradiation of the proposed characteristics (see "Testing the hypothesis" section) causes only minor elevation in tissue temperature (see Suppl. Materials Figure S1). Thus, integrating pulsed UVC into a laser bronchoscope as a delivery tool, should be sufficient to reach the lungs and inactivate the virus (Figure 1).

The tracheobronchial tree is an arrangement of branching tubes, which is composed of the trachea and bronchi of different diameters. Since the external diameter of traditional bronchoscopes is generally 5 to 6 mm, these devices cannot easily penetrate fourth- to fifth-order subsegmental bronchi in adults [29]. However, there are ultrathin bronchoscopes with much smaller external diameters (<3 mm), which may reach the subsegmental bronchi of even sixth-order [29,30]. Thus, UVC irradiation could potentially cover most volume of the lung tissue. Considering the fact that there are less than forty fifth-order bronchi [30], and that the suggested duration of UVC irradiation for each subsegmental bronchus should not exceed 30 seconds, the maximum time of treatment will take from 20 to 30 min. Moreover, CT-based studies show that SARS-CoV-2 is concentrated in specific areas in the lungs ("hotspots") even in patients with severe or critical illness [31]. Thus, combining the use of ultrathin bronchoscope with CT-scan outputs, could efficiently direct UVC treatment into those hotspots, without the need to treat large areas of the lungs. Remarkably, a CT-scan-based deep learning model has been developed, which could predict COVID disease progression and highlight the hotspots influencing the severity of the disease [32]. This tool could further direct the UVC treatment more accurately.

Of note, although we propose UVC primarily as a prophylactic measure against the fibroproliferative conditions, it might also serve as a treatment of post COVID-19 pulmonary fibrosis. This assumption are positive results of UV treatment (UVA and UVB) of various forms of fibrosis, such as nephrogenic systemic fibrosis and scleroderma [33–35].

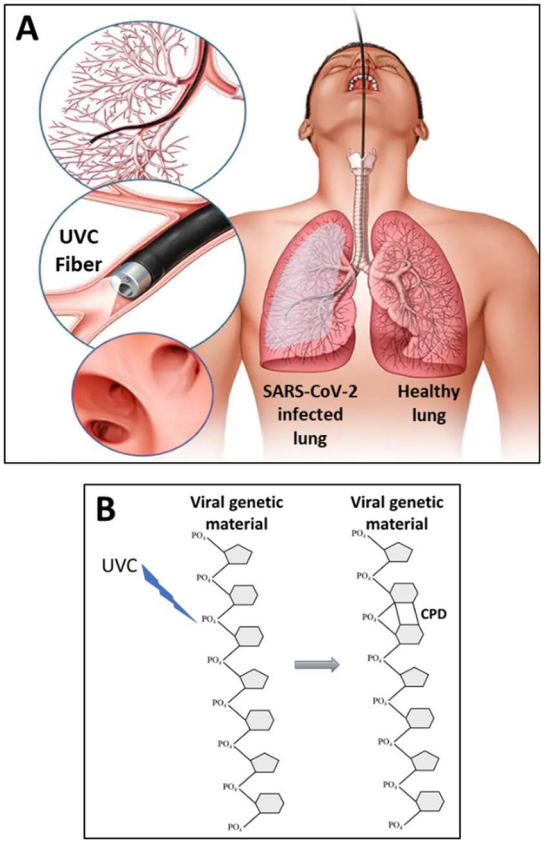

Figure 1. Schematic presentation of (**A**) the treatment modality for pulsed-UVC irradiation of SARS-CoV-2 infected lung by laser bronchoscopy, and (**B**) the mechanism of UVC antiviral activity. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

4. Safety Issues

Regarding the safety concerns in applying such a method, two important points must be considered: (i) Most of the available data on the germicidal effect of continuous UVC refers to a 254-nm wavelength (reviewed at [18]), since it is the peak of the conventional germicidal curve. However, as shown in Table 1, more and more studies have demonstrated that continuous far-UVC (207–222 nm) inactivates pathogens as efficiently as the conventional 254 nm [20–21,28,36–38], without harming the exposed normal skin tissues in mice [38–43] and human skin [44–47]. All these studies specifically recommend the use of filtered far-UVC only, as it is much safer than the conventional 254 nm UVC. Although most studies evaluated short-term effects, Yamano et al. (2020) did not observe any long-term DNA damage (CPD formation) or tumor development after repetitive or even chronic 222-nm UVC irradiation of mice at a dose of 100 mJ/cm^2. Only slight increase in DNA damage was recognized in the uppermost part of the epidermis and the sub-corneal region after high dose irradiation of 500 mJ/cm^2. Remarkably, no erythema, ear swelling, or inflammatory response occurred even after exposure to much higher doses of up to 1000 mJ/cm^2. In contrast, a 254-nm UVC irradiation induced all the above pathological conditions even at 100 mJ/cm^2 [40]. Of note, the sterilizing dose is estimated to be 10 mJ/cm^2 [25]. In brief, it seems that using far-UVC of 222 nm wavelength should minimize the risks connected to the clinical use of UVC. (ii) The dose required for SARS-CoV-2 inactivation is rather low. Kitagawa et al. [21] showed *in vitro* that several seconds of a 222-nm UVC irradiation with a total dose of 1 or 3 mJ/cm^2 resulted in 88.5% and 99.7% reduction of viable SARS-CoV-2, respectively. Of note, the regulatory total dose limit of a 222-nm UV irradiation for the public is one order higher (approximately 23 mJ/cm^2) [48]. Studies on both humans and mice, some with highly photocarcinogenic phenotype, displayed only a slight risk to skin tissue at 3-orders higher total dose, and no risk at 1–2 orders higher total doses (Table 1). Either way, CPD generation in the human skin cells is estimated to occur daily, especially when staying outdoors for 20 min on a sunny day [49]. Of course, a direct extrapolation from skin to lung tissue should be done with caution. Yet, it is estimated that infected person carries 10^9 to 10^{11} virions during peak infection, from which at least 90% are in the lungs [50]. A good estimation of the infectious yield of SARS-COV-2 is ~10 to 100 infectious units per cell [50]. This greatly increases the chance that UVC will target SARS-COV-2 virions, relatively to lung cells. Moreover, Buonanno et al (2017) proposed that far-UVC is much likely to hit the viruses (which are much smaller in size than human cells) rather than nuclear DNA, as UVC is strongly absorbed by the proteins in the cytoplasm and drastically attenuated before reaching the nucleus [38]. The safety of UVC treatment has also been shown in lungs [51,52]. Specifically, the lungs of HCV-positive donors were exposed ex vivo to UVC of 254 nm for 4–6 h before transplantation, in order to prevent HCV

transmission to recipient. The results showed no lung injury after UVC irradiation, with a significant decrease in HCV viral loads after transplantation [51]. Recently, a clinical trial was conducted to test the endotracheal application of UVA in patients with SARS-CoV-2. The patients were treated daily with UVA emission of maximum 2 mW/cm^2, which was delivered for 20 min for 5 days, with a month follow-up. The results show a clear reduction of SARS-CoV-2 viral load with no significant adverse outcomes [52]. From the analysis above, we hypothesize that the application of pulsed far-UVC could provide a therapeutic value for patients with a severe form of COVID-19, which is much higher than irradiation risk.

Table 1. Conventional UVC characteristics used in clinical trials and *in vivo* experiments on mice. All experiments used a 222-nm UVC light on skin except for the work done by Buonanno et al. [41], where a 207 nm wavelength was used.

Type of the Test	Intensity (μW/cm^2)	Total Dose (mJ/cm^2)	Biological Outcome	Ref.
Clinical trial	5800	Up to 18,000	No erythema; no long-lasting coloring of the skin.	[44]
Clinical trial	N.D.	6100	Slight CPD [a] formation only in the upper layers of the epidermis.	[45]
Clinical trial	5500	50–500	Slight increase in CPD [a] formation.	[47]
Clinical trial [b]	6000	540	No complications or side-effects.	[46]
In vivo	6.2	157	No epidermal thickness; no keratinocyte proliferation or differentiation; no increase in DNA photodamage; no skin inflammation.	[38]
In vivo	3500	40; 300	No epidermal thickness; no DNA photodamage.	[41]
In vivo [c]	1000	100–1000	No short or long-term tumors; no DNA damage; no erythema; no ear swelling; no inflammatory response; slight CPD [a] formation in the uppermost layer of the epidermis at high intensity; no significant changes on retinal tissue.	[40]
In vivo	3000	450	No mutagenic or cytotoxic effects in the epidermis.	[39]
In vivo [d]	3000	450	No CPD-expressing cells in either epidermis or dermis; faster wound healing.	[53]
In vivo	6.2	157	No epidermal thickness; no keratinocyte proliferation or differentiation; no increase in UV-induced DNA photodamage; no skin inflammation.	[42]

[a] CPD indicates a carcinogenic risk; [b] UVC was applied to treat skin bedsores (pressure ulcers); [c] Eye was also examined; [d] UVC was applied to treat skin wounds.

5. Testing the Hypothesis

To examine the hypothesis, we suggest the integration of pulsed UVC technology into a laser bronchoscope. Although lab experiments and pre-clinical trials should be done in order to establish the exact characteristics of pulsed UVC irradiation for treating the COVID-19 infection, as well as the penetrability of pulsed UVC, based on the available data, we suggest using a 222 nm band-passed filter light with intensity of up to 200 μW/cm^2, and a total delivery which should not exceed 500 mJ/cm^2. This dose is much lower than the clinically tested UVA treatment for SARs-CoV-2 [52]. Other specific characteristics, such as UVC source, frequency, etc. would have to be determined during lab experiments. We believe that this combination might present minimal (if any) hazard to humans, as presented in both clinical trials and *in vivo* experiments on mice. Nonetheless, we suggest using this treatment only for patients with a severe form of COVID-19. Such a therapeutic method might greatly contribute to the world's efforts in dealing with this threat. As the great Hippocrates already said in his Aphorisms: "*For extreme diseases, extreme methods of cure, as to restriction, are most suitable*".

Supplementary Materials

The supporting information can be found at: https://www.sciepublish.com/index/journals/article/fibrosis/32.html/id/22.

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Author Contributions

E.D. is the author of this idea. The concept was further developed with participation of V.E.F. and E.D. and discussed with M.W. and A.K. who also conducted the preliminary calculations of UVC parameters. E.D. and V.E.F. wrote the manuscript with participation of M.W. and A.K. All authors reviewed the manuscript. Visualization, E.D. and A.K.; Supervision, V.E.F.; Funding Acquisition, A.K. and V.E.F.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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