Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Photobiomodulation therapy and antimicrobial photodynamic therapy for orofacial lesions in patients with COVID-19: A case series

Inessa Solek Teixeira [a], Fidel Silveira Leal [b], Ricardo Yudi Tateno [c], Luiz Felipe Palma [d], Luana Campos [c,*]

[a] Imperial Charity Hospital, Florianópolis, SC, Brazil
[b] Department of Cardiology, School of Medicine, University of São Paulo, São Paulo, SP, Brazil
[c] Graduate Program in Implantology, University of Santo Amaro, School of Dentistry. São Paulo, SP, Brazil
[d] Graduate Dentistry Program, Ibirapuera University, São Paulo, SP, Brazil

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ABSTRACT

Oral lesions related to the novel Coronavirus Disease 2019 (COVID-19) have been increasingly described; however, clinical and epidemiological information is still scant. Although a diversity of therapeutic strategies for the management of these lesions are present in the literature, one can note a lack of standardization and doubtful effectiveness. Thus, the present study aimed to report a series of cases in which a combination of antimicrobial photodynamic therapy (aPDT) and photobiomodulation therapy (PBMT) was used for orofacial lesions in patients suffering from COVID-19. It was noted, in all cases, a marked improvement in tissue repair and pain relief within a few days; moreover, the patients recovered their orofacial functions satisfactorily. Based on the present series of cases and having in mind the conspicuous lack of information on the different aspects of COVID-19, the protocol which combined aPDT with PMBT seemed to be effective in the management of COVID-19-related orofacial lesions.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2, a single-chain RNA virus, is responsible for the novel Coronavirus Disease 2019 (COVID-19) pandemic [1]. According to the World Health Organization website on 19 February 2021, almost 110 million cases of COVID-19 have been confirmed globally since the start of the pandemic, resulting in over 2 million deaths [2].

A very recent study reported a frequency of oral lesions in patients with COVID-19 of 78.4 % [3]; however, clinical and epidemiological information is still scant in the literature [4]. Some therapeutic strategies such as mouthwashes, topical or systemic drugs (antifungals, antibiotics, antivirals, corticosteroids), and even photobiomodulation therapy (PBMT) singly [1] or in combination with antimicrobial photodynamic therapy (aPDT) [5] have been used empirically for treating these orofacial lesions, presenting varying effectiveness.

In light of these facts, the present study aims to report a series of clinical cases in which PBMT and aPDT were used to manage orofacial lesions in patients suffering from COVID-19.

1.1. Case 1

A Brazilian 57-year-old male, with a history of well-controlled hypertension, sought medical help owing to headache, myalgia, and dyspnea. The patient was diagnosed with COVID-19 by the real-time reverse transcription-polymerase chain reaction (RT-PCR) test, and hospitalized with the initial treatment proposal including azithromycin and ceftriaxone; however, after about 12 days, he had to be sent to the Intensive Care Unit (ICU) for endotracheal intubation and mechanical ventilation, lasting 10 days. Besides supportive measures, dexamethasone was administered, as well as piperacillin with tazobactam for *Candida albicans* present in urine culture and multi-resistant *Pseudomonas aeruginosa* in tracheal secretion culture.

Approximately 4 days after extubation, it was noted a painful lip lesions covered by crust, which were then removed and caused bleeding (Fig. 1A). An association of aPDT and PBMT was performed and repeated on the following day. For PBMT, a laser device Laser DUO® (MMOptics, São Carlos, SP, Brazil) was used at 660 nm, on contact mode, point by point, with 100 mW, 33 J/cm2, 0.5 J, and 5 s per point. A

* Corresponding author at: School of Dentistry, University of Santo Amaro, Rua Prof. Enéas de Siqueira Neto, 340 - Jardim das Imbuias, São Paulo, SP, 04829-300, Brazil.
E-mail address: lucampos@prof.unisa.br (L. Campos).

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total of 6 points were distributed throughout the lesions. Shortly thereafter, an aPDT technique was performed, with methylene blue at 0.01 % applied over all lesions, and after 3 min (time pre-irradiation), the same laser parameters were used, but delivering 40 s (4 J) per lesion. There was a marked improvement in healing within 24 hours (Fig. 1B). After 72 hours, the lesions were no longer present (Fig. 1C).

1.2. Case 2

A Brazilian 84-year-old female, with a history of hypertension, hypothyroidism, and rectal tumor, sought medical help owing to a flu-like syndrome suggestive of COVID-19. The patient had been submitted to intestinal surgery in the previous month and had been discharged from the hospital only a day before the readmission. The RT-PCR test confirmed the clinical suspicion.

According to the isolation of *Enterococcus faecalis* by haemoculture, piperacillin and tazobactam were administered; however, they were later replaced by ampicillin. Approximately 10 days after the hospital readmission, it was noted two painful lesions on both lips, showing small ulcered areas (Fig. 1D,E). As a treatment, the same protocol for PBMT and aPDT described in case 1 was performed. In 24 h, the lesion was fully healed (Fig. 1F).

1.3. Case 3

A Brazilian 70-year-old female, with a history of well-controlled hypertension, dyslipidemia, and hypothyroidism, sought medical help owing to a flu-like syndrome suggestive of COVID-19. The RT-PCR test confirmed the clinical suspicion.

Eighteen days after the first symptoms of COVID-19, even receiving azithromycin and ceftriaxone/cefuroxime, she rapidly developed severe and progressive dyspnea, resulting in acute respiratory failure. Thus, the patient was sent to the ICU for endotracheal intubation and mechanical ventilation, lasting approximately 11 days. She developed a bacterial infection (*Klebsiella Pneumoniae Carbapenemase*) and received meropenem and vancomycin. It was noted fungal infections in the skin (several areas) and oral mucosa (*Candida albicans*), which were treated with topical nystatin.

Likewise, painful lesions on lips arose and the patient received systemic acyclovir considering the likelihood of a herpes simplex virus type 1 infection (Fig. 1G). Once the lesions did not respond well to the antiviral agents, so the same aPDT and PBMT protocol (described in case 1) were proposed, daily (Fig. 1H). Healing was improved within 3 days and the patient no longer reported pain (Fig. 1I).

1.4. Case 4

A Brazilian 64-year-old female, with a history of well-controlled

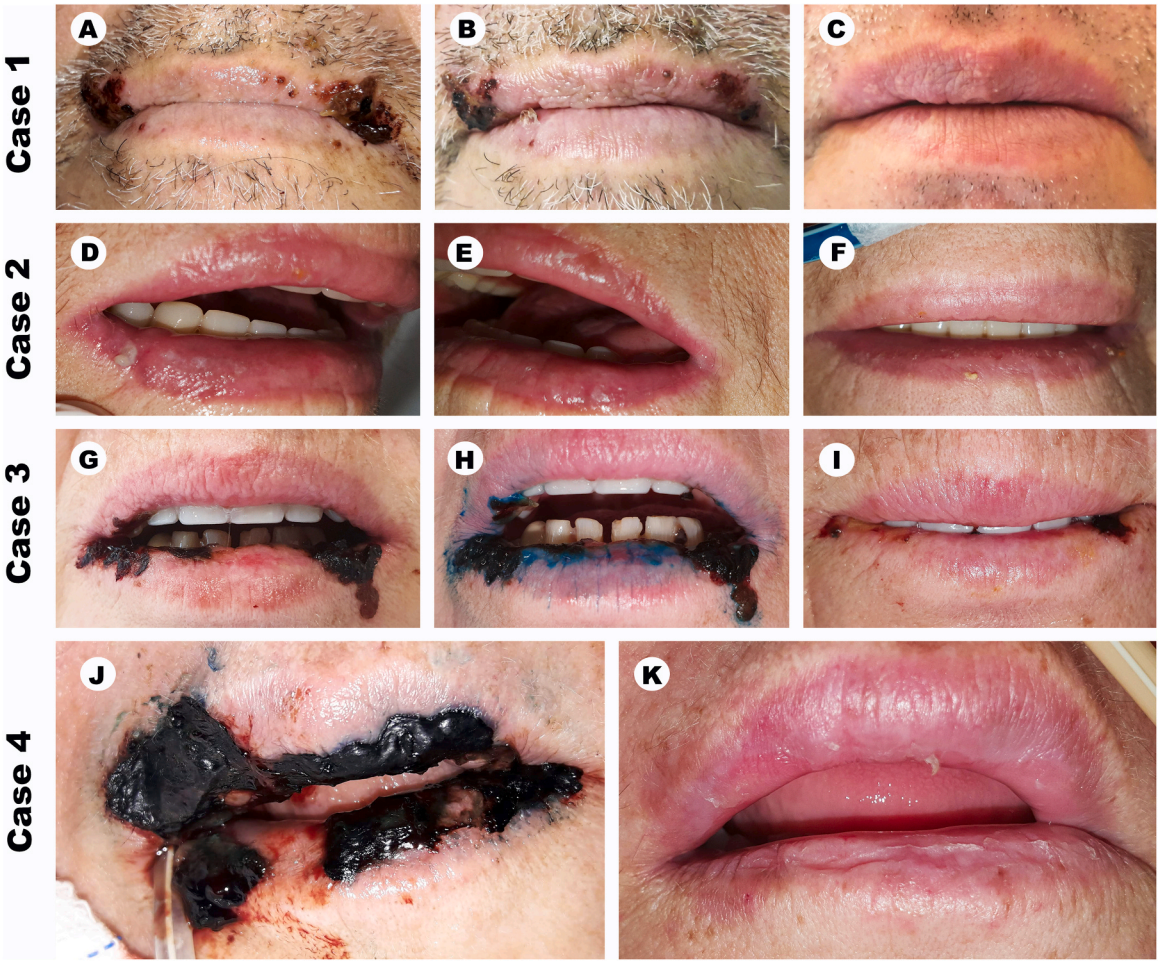

Fig. 1. (A) case 1 initial clinical presentation, showing the lip lesions covered by crust, (B) 24 h after phototherapies, (C) 72 h after phototherapies, (D) case 2 initial clinical presentation, showing a small lip lesion – right side, (E) initial clinical presentation, showing a small lip lesion – left side ini, (F) 24 h after phototherapies, (G) case 3 initial clinical presentation, showing lip lesions covered by crust, (H) methylene blue applied onto oral mucosa for aPDT technique, (I) 72 h after phototherapies, (J) case 4 initial clinical presentation, (K) 4 days after phototherapies.

hypertension, obesity, bipolar disorder, and hypothyroidism, sought medical help owing to dry cough, nausea, hypoxia, fever for 7 days, dyspnea, odynophagia, and nasal congestion. The RT-PCR test confirmed the diagnosis of COVID-19.

Nineteen days after the first symptoms, even receiving azithromycin and ivermectin, she rapidly developed severe and progressive pneumonia. Thus, after being sent to the ICU for endotracheal intubation and mechanical ventilation, within 30 days was noted painful and extensive lip lesions covered by crust (Fig. J). Just after clinical evaluation and diagnosis, the same aPDT and PBMT protocol (described in case 1) were proposed, also daily. However, due to the greater extent of the lesions, more irradiation points were used: 5 points of 4 J on the upper lip and 5 on the lower lip. The complete tissue repair was achieved in 4 days (Fig. 1K).

2. Discussion

In the cases presented, the association of aPDT and PBMT resulted in an important clinical improvement of the patients' orofacial condition within few days. To the best of the authors' knowledge, only two papers have previously addressed the use of these techniques to treat orofacial lesions in patients suffering from COVID-19. Brandão et al. [6] presented some clinical cases in which the PBMT sessions lasted 10 consecutive days but not all lesions responded satisfactorily to the light approach; however, Ramires et al. [5] combined aPDT and PBMT in extensive lip lesions during a total of 2 days and the patient showed complete healing at the fourth day.

The light protocol applied herein relies on that aPDT is considered to be highly effective in the treatment of opportunistic infections of the oral cavity (including virucidal activity against viruses with an envelope such as the coronaviruses) and that PBMT can reduce or inhibit substances that play important roles in pain and inflammatory processes [5]. Even given the complexity of the referred cases, aPDT and PBMT were shown to be safe and effective in both controlling and treating orofacial lesions in patients who were presenting the signs and symptoms of COVID-19 in different degrees of severity. Furthermore, the technique was simple to perform in a hospital setting and was neither time-consuming nor expensive.

Concerning the study limitations, case series with no comparison group are ranked at the lowest level of evidence. This kind of study, however, is still highly necessary, especially on COVID-19, since it may provide clinicians early information and novel insights for evolving illnesses. During the rapidly evolving global pandemic experienced today, any study should not be dismissed, as the entire process of developing, carrying out, and publishing the findings of a high-quality study may delay the spread of quite needed data [7].

Based on the present series of cases and having in mind the conspicuous lack of information on the different aspects of COVID-19, the protocol which combined aPDT with PMBT seemed to be effective in the management of COVID-19-related orofacial lesions.

References

[1] B. Iranmanesh, R. Amiri, H. Zartab, M. Aflatoonian, Oral manifestations of COVID -19 disease: a review article, Dermatol. Ther. (2020), https://doi.org/10.1111/dth.14578.
[2] World Health Organization, WHO Coronavirus Disease (COVID-19) Dashboard, 2021 (accessed February 19, 2021), https://covid19.who.int.
[3] V. Fidan, H. Koyuncu, O. Akin, Oral lesions in Covid 19 positive patients, Am. J. Otolaryngol. 42 (2021), 102905, https://doi.org/10.1016/j.amjoto.2021.102905.
[4] J. Amorim dos Santos, A.G.C. Normando, R.L. Carvalho da Silva, A.C. Acevedo, G. De Luca Canto, N. Sugaya, A.R. Santos-Silva, E.N.S. Guerra, Oral manifestations in patients with COVID-19: a living systematic review, J. Dent. Res. (2020), https://doi.org/10.1177/0022034520957289.
[5] M.C.C.H. Ramires, M.B. Mattia, R.Y. Tateno, L.F. Palma, L. Campos, A combination of phototherapy modalities for extensive lip lesions in a patient with SARS-CoV-2 infection, Photodiagnosis Photodyn. Ther. (2021), 102196, https://doi.org/10.1016/j.pdpdt.2021.102196.
[6] T.B. Brandão, L.A. Gueiros, T.S. Melo, A.C. Prado-Ribeiro, A.C.F.A. Nesrallah, G.V. B. Prado, A.R. Santos-Silva, C.A. Migliorati, Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? Oral Surg. Oral Med. Oral Pathol. Oral Radiol. (2020) https://doi.org/10.1016/j.oooo.2020.07.014.
[7] I. Ikuta, Level of evidence during the COVID-19 pandemic: making the case for case series and case reports, Am. J. Neuroradiol. 41 (2020) 1646, https://doi.org/10.3174/ajnr.A6676.