

Photodynamic therapy and Photobiomodulation as adjuvant treatment of oral and facial manifestations in patients with COVID-19 hospitalized in the intensive care unit: a case series

Terapia Fotodinâmica e Fotobiomodulação como tratamento adjuvante em manifestação oral e facial em pacientes com COVID-19 hospitalizados em uma unidade de terapia intensiva: uma série de casos

Terapia Fotodinámica y Fotobiomodulation como tratamiento adyuvante de la manifestación oral y facial en pacientes con COVID-19 hospitalizados en una unidad de cuidados intensivos: una serie de casos

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Abstract

Orofacial injuries resulting from Coronavirus-19 (COVID-19) are reported in the current literature. The etiology of these manifestations is still unknown, but them seem to have an association between the prone position and patient's immunosuppression. Clinical features range from nonspecific ulcers to vesicles that may mimic viral infections. The search for a clinical protocol for the cure of these lesions is necessary. Thus, some studies about photobiomodulation, a low-level light therapy with regenerative tissue action, associated with antimicrobial photodynamic therapy, as a promising adjuvant treatment. Therefore, the present study aims to report a series of cases where photobiomodulation and photodynamic therapy were used in patients positive for COVID-19 and presented orofacial lesions during the time of hospitalization in the intensive care unit. In all cases, tissue regeneration was complete, demonstrating the

effectiveness of photobiomodulation and photodynamic therapy as adjuvant therapy associated with the use of medicines.

Keywords: Coronavirus; Low-Level light therapy; Methylene blue; Prone position, Hospitalization.

Resumo

Lesões orofaciais decorrentes do Coronavírus-19 (COVID-19) são reportados na literatura atual. A etiologia dessas manifestações ainda é desconhecida, mas aparentam ter associação da posição de prona com o quadro de imunossupressão do paciente. As características clínicas variam de úlceras não específicas a vesículas que mimetizam infecções virais. A procura por um protocolo clínico para a cura dessas lesões é necessário. Dessa forma, alguns estudos apontam a fotobiomodulação, uma terapia de laser com baixa intensidade com ação tecidual regenerativa, associada a terapia fotodinâmica antimicrobiana, como um tratamento adjuvante promissor. Portanto, o presente estudo tem como objetivo relatar uma série de casos onde a fotobiomodulação e terapia fotodinâmica foram utilizadas em pacientes positivados para COVID-19 e que apresentaram lesões orofaciais durante o tempo de internação na unidade de terapia intensiva. Em todos os casos, a regeneração tecidual foi completa, demonstrando a efetividade da fotobiomodulação e terapia fotodinâmica como terapia adjuvante associada ao uso de medicamentos.

Palavras-chave: Coronavírus; Terapia com luz de baixa intensidade; Azul de metileno; Decúbito ventral; Hospitalização.

Resumen

Las lesiones orofaciales resultantes del Coronavirus-19 (COVID-19) se informan en la literatura actual. La etiología de estas manifestaciones aún se desconoce, pero parecen tener una asociación entre el decúbito prono y la inmunosupresión del paciente. Las características clínicas van desde úlceras inespecíficas hasta vesículas que simulan infecciones virales. Es necesaria la búsqueda de un protocolo clínico para la curación de estas lesiones. Así, algunos estudios apuntan a la fotobiomodulación, una terapia láser de baja intensidad con acción regeneradora de tejidos, asociada a la terapia fotodinámica antimicrobiana, como un prometedor tratamiento adyuvante. Por lo tanto, el presente estudio tiene como objetivo reportar una serie de casos donde se utiliza fotobiomodulación y terapia fotodinámica en pacientes positivos para COVID-19 y que presentaron lesiones orofaciales durante el tiempo de hospitalización en la unidad de cuidados intensivos. En todos los casos la regeneración tisular fue completa, demostrándose la eficacia de la fotobiomodulación y la terapia fotodinámica como terapia adyuvante asociada al uso de fármacos.

Palabras clave: Coronavirus; Terapia por luz de baja intensidad; Azul de metileno; Posición prona; Hospitalización.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disorder responsible for the severe acute respiratory syndrome (SARS) and, may cause a long period of hospitalization, increase of risk of death and significant decrease of quality of life (Ahmed et al., 2020; Jacobs et al., 2020). Not least, some oral manifestations such as taste disturbances, nonspecific oral ulcerations, desquamative gingivitis, petechiae and opportunistic infections may be present and collaborate to general clinical status of the patient (Brandão et al., 2021). To assist in the healing process, photobiomodulation (PBMT) and/or antimicrobial photodynamic therapy (aPDT) have been implemented as adjuvant treatment in orofacial cases probably caused by COVID-19 (Amorim dos Santos et al., 2020; Bhujel et al., 2021; Brandão et al., 2021; Ramires et al., 2021; El Kady et al., 2021; Perrillat et al., 2020; Ramalho et al., 2021; Solek et al., 2020).

PBMT is the therapeutic action of light absorbed by endogenous chromophores that trigger painless biological reactions which promote physiological changes in favor of tissue homeostasis (Dompe et al., 2020). Especially in situations of tissue aggression, PBMT promotes significant benefits, such as inflammatory reduction, acceleration of tissue regeneration, prevention of fibrosis, reduction of pain and edema (Meneguzzo et al., 2013).

In aPDT, photosensitizers as methylene or toluidine blue, with concentrations of 0.01% or 0.005% are used in resonance with red laser light, generating reactive oxygen species highly toxic to microorganisms (Christina et al., 2020; La Selva et al., 2020; Ramalho et al., 2021).

2. Methodology

It is a clinical case series with a descriptive and qualitative approach (Estrela, 2018). In this article, four clinic cases of patients who had extensive lesions in facial and oral cavity possibly caused by COVID-19, submitted to application of PBMT and aPDT with a variable number of points dependents of the lesion size are described.

This study was submitted and approved by São Leopoldo Mandic College Ethical committee and received the approval number 53872221.8.0000.5374.

3. Results

Case 1

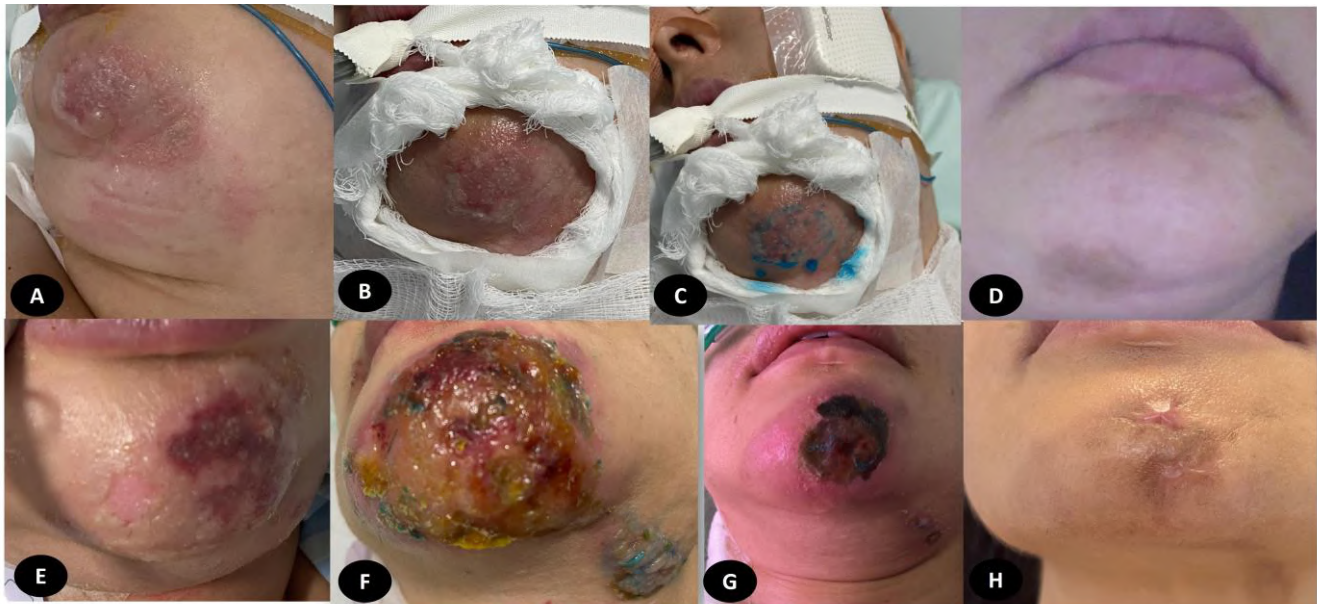
A 38-year-old female patient with COVID-19 was admitted to the intensive care unit (ICU) with 50% of pulmonary involvement. Orotracheal intubation (OTI) was performed in association with 32 hours prone position.

After pronation, multiple vesicles were observed in mental region (Fig 1A). Concomitant with the use of Acyclovir intravenous (IV) (250mg) and Dexamethasone IV (10 mg), 7 consecutives daily aPDT sessions with 660 nm, on contact mode, point by point, with 100 mW, 32.14 J/cm², 9J and 90 s per point were made with Therapy EcR (DMC, São Carlos, SP, Brazil). A pre-radiation of 0.01% methylene blue (Chimiolux, DMC, São Carlos, SP, BR) for 5 minutes was carried out covering the entire lesion after vesicular rupture with a sterile needle (40x12) (Fig 1B/C). During aPDT treatment, the formation of crusted areas was noted. After the 17th session, PBMT with 600 and 808 nm, on contact mode, point by point, with 100mW, 17.8 J/cm² 1 J, and 10 s for irradiation per point was performed around the crust, on consecutive days, in 3 sessions with the same equipment, until the complete remission of the lesion (Fig 1D).

Case 2

A 40-year-old female patient, diagnosed with COVID-19, was admitted to the ICU with 75% of pulmonary involvement. OTI with pronation was performed for 5 alternative days, with a total of 18 hours each day. In the lower third of the face, an ulcerative lesion with multiple vesicles surrounded by an erythematous area associated with a pressure lesion was noted (Fig. 1E/F). Acyclovir IV (250 mg) and Dexamethasone IV (10 mg) were administered, and 10 aPDT sessions were performed on consecutive days following the same protocol described in case 1. After improvement of the ulcerated lesion, 2 sessions of PBMT were made using the same protocol in case 1 as well (Fig. 1G/H).

Figure 1. Case 1. (A/B) Initial presentation of the lesion; (C) Methylene blue applied over the lesion; (D) 10 days after the performance of aPDT and PBMT. **Case 2.** (E) Initial presentation of the lesion; (F) Methylene blue applied over the lesion; (G) Crust formation after performing aPDT and PBMT; (H) Complete resolution of the condition after 12 days of laser therapy.



Source: Authors.

Case 3

A 34-year-old male patient with a 75% of pulmonary involvement underwent to OTI because of signs and symptoms of COVID-19. He developed 2 ulcerated lesions with hemorrhagic central areas surrounded by crusts and vesicles extending from skin of lateral nose wing to zygomatic area similar to prone position or viral infection (Fig. 2A). Acyclovir IV (250 mg) was prescribed, and Methylprednisolone IV (40 mg) was already being used. In sequence, the same adjuvant therapy protocol of the previous cases was started (Fig. 2B). 5 sessions of aPDT were performed and, after that, 3 sessions of PBMT, with an important healing was observed (Fig. 2C).

Case 4

A 62-year-old male patient was admitted to the ICU and underwent to OTI due pulmonary complications of COVID-19. The prone position was implemented during 16 hours over a period of 5 alternative days. The intraoral physical examination revealed the presence of crusted and bleeding lesions in the palate, bilateral buccal mucosa, bilateral labial commissure, and upper and lower lips. The same pattern was observed in the region of the right and left face, chin and nose (Fig. 2D/E/F). Besides, Acyclovir IV (250 mg) and Methylprednisolone IV (125 mg) were prescribed. Additionally, the same protocol of aPDT and PBMT used in the previous cases was performed, observing total remission of the condition (Fig. 2G).

Figure 2. Case 3. (A) Initial presentation of the lesion; (B) After the first aPDT session (C) After 5 aPDT session. **Case 4.** (D/E/F) Ulcerated and crusted lesions; (G) After all applications of aPDT and PBMT.



Source: Authors.

4. Discussion

Orofacial manifestations associated with COVID-19 have been described in the literature (Amorim dos Santos et al., 2020; Berlingieri et al., 2022; Bhujel et al., 2020; Brandão et al., 2021; El Kady et al., 2021; Perrillat et al., 2020). The exacerbation of these lesions is probably related to time and non-movement during the prone position because it is important to increase respiratory volume and, consequently, to improve the condition of patients with SARS undergoing OTI (Moore et al., 2020; Perrillat et al., 2020).

The chronic use of medications such as corticosteroids improve the clinical condition of SARS, but may suppress the immune system and facilitate the emergence of infections, mainly herpes simplex virus, cytomegalovirus and candidiasis (Brandão et al., 2021; Ochani et al., 2021; Raman et al., 2021; Solek et al., 2020; Lotfi et al., 2020). All patients treated in this article were under corticosteroids treatment for a considerable time and developed lesions clinically compatible with viral infections that may be intensified with the presence of COVID-19. Despite the ulcerated lesions have not been tested for the presence of virus, aPDT is known to be an important adjunct therapy against virus, bacteria, and fungus infections (Berlingieri et al., 2022).

To date, few articles have shown results obtained using aPDT and/or PBMT in cases of orofacial lesions associated with COVID-19 (Brandão et al., 2021; Garcez et al., 2021; Teixeir et al., 2021). The protocol recommended for PBMT followed that carried out in two other case reports based on consolidated studies about antimicrobial, antifungal and antiviral action (Christina et al., 2020; Teixeira et al., 2021).

Additionally, aPDT and PBMT are non-invasive techniques that may be used safely in patients with a wide range of underlying diseases and comorbidities because of their high decontamination capacity (Pacheco et al., 2022). Furthermore, it is important to emphasize the use of medications and other types of treatment associated with this adjunct therapy in orofacial ulcerated lesions in hospitalized patients, as example, Acyclovir (Teixeira et al., 2021). In these current cases, no side effects with aPDT and PBMT were observed, and positive effects were noted in a short period of time.

5. Conclusion

The association of PBMT and aPDT proved to be an adjuvant effective treatment and may be implemented by health services, because the healing of these lesions improves the quality of life of hospitalized patients. Thus, it's important to have more studies about the laser efficiency in this kind of lesions related to COVID-19.

References

- Ahmed, H., Patel, K., Greenwood, D. C., Halpin, S., Lewthwaite, P., Salawu, A., Eyre, L., Breen, A., O'Connor, R., Jones, A., & Sivan, M. (2020). Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. *Journal of Rehabilitation Medicine*, 52(5), 1-11.
- Amorim dos Santos, J., Normando, A. G. C., Carvalho da Silva, R. L., De Paula, R. M., Cembranel, A. C., Santos-Silva, A. R., & Guerra, E. N. S. (2020). Oral mucosal lesions in a COVID-19 patient: New signs or secondary manifestations? *International Journal of Infectious Diseases*, 97, 326–328.
- Berlingieri, G., Maria, C., Alvares, A., Verardi, R., Felipe, L., & Campos, L. (2022). Phototherapies for COVID-19 associated opportunistic oral infections. *Photodiagnosis and Photodynamic Therapy*, 37, 1-2.
- Bhujel, N., Zaheer, K., & Singh, R. P. (2021). Oral mucosal lesions in patients with COVID-19: a systematic review. *Br J Oral Maxillofac Surg*. 2021; 59(9):1024-1030.
- Brandão, T. B., Gueiros, L. A., Melo, T. S., Prado-Ribeiro, A. C., Nesrallah, A. C. F. A., Prado, G. V. B., Santos-Silva, A. R., & Migliorati, C. A. (2021). Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 131(2), e45–e51.
- Dompe, C., Moncrieff, L., Matys, J., Grzech-Leśniak, K., Kočerova, I., Bryja, A., Bruska, M., Dominiak, M., Mozdziak, P., Skiba, T., Shibli, J. A., Angelova Volponi, A., Kempisty, B., & Dyszkiewicz-Konwińska, M. (2020). Photobiomodulation-Underlying Mechanism and Clinical Applications. *Journal of clinical medicine*, 9(6), 1724.
- El Kady, D. M., Gomaa, E. A., Abdella, W. S., Ashraf Hussien, R., Abd ElAziz, R. H., & Khater, A. (2021). Oral manifestations of COVID-19 patients: An online survey of the Egyptian population. *Clinical and experimental dental research*, 7(5), 852–860.
- Estrela, C. (2018). *Metodologia científica: ciência, ensino, pesquisa*. 3.ed. Porto Alegre: Artes Médicas.
- Garcez, A. S., Delgado, M. G. T., Sperandio, M., Dantas E Silva, F. T., De Assis, J. S. R., & Suzuki, S. S. (2021). Photodynamic Therapy and Photobiomodulation on Oral Lesion in Patient with Coronavirus Disease 2019: A Case Report. *Photobiomodulation, Photomedicine, and Laser Surgery*, 39(6), 386–389.
- Jacobs, L. G., Paleoudis, E. G., Bari, D. L. Di, Nyirenda, T., Friedman, T., Gupta, A., Rasouli, L., Zetkucic, M., Balani, B., Ogedegbe, C., Bawa, H., Berrol, L., Qureshi, N., & Aschner, J. L. (2020). Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. *PLoS ONE*, 15(12), 1–14.
- La Selva, A., Negreiros, R. M., Bezerra, D. T., Rosa, E. P., Pavesi, V. C. S., Navarro, R. S., Bello-Silva, M. S., Ramalho, K. M., Aranha, A. C. C., Braz-Silva, P. H., Fernandes, K. P. S., Bussadori, S. K., & Horliana, A. C. R. T. (2020). Treatment of herpes labialis by photodynamic therapy. *Medicine*, 99(12), 1-9.
- Lotfi, M., Hamblin, M. R., & Rezaei, N. (2020). COVID-19: Transmission, prevention, and potential therapeutic opportunities. *Clinica chimica acta; international journal of clinical chemistry*, 508, 254–266.
- Meneguzzo, D. T., Lopes, L. A., Pallota, R., Soares-Ferreira, L., Lopes-Martins, R. Á., & Ribeiro, M. S. (2013). Prevention and treatment of mice paw edema by near-infrared low-level laser therapy on lymph nodes. *Lasers in medical science*, 28(3), 973–980.
- Moore, Z., Patton, D., Avsar, P., McEvoy, N. L., Curley, G., Budri, A., Nugent, L., Walsh, S., & O'Connor, T. (2020). Prevention of pressure ulcers among individuals cared for in the prone position: Lessons for the COVID-19 emergency. *Journal of Wound Care*, 29(6), 312–320.
- Ochani, R. K., Asad, A., Yasmin, F., Shaikh, S., Khalid, H., Batra, S., Sohail, M. R., Mahmood, S. F., Ochani, R., Arshad, M. H., Kumar, A., & Surani, S. (2021). Covid-19 pandemic: From origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management. *Infezioni in Medicina*, 29(1), 20–36.
- Pacheco, J. A., Molena, K. F., Martins, C., Corona, S., & Borsatto, M. C. (2022). Photobiomodulation (PBMT) and antimicrobial photodynamic therapy (aPDT) in oral manifestations of patients infected by Sars-CoV-2: systematic review and meta-analysis. *Bulletin of the National Research Centre*, 46(1), 140.
- Perrillat, A., Foletti, J. M., Lacagne, A. S., Guyot, L., & Graillon, N. (2020). Facial pressure ulcers in COVID-19 patients undergoing prone positioning: How to prevent an underestimated epidemic?. *Journal of stomatology, oral and maxillofacial surgery*, 121(4), 442–444.
- Ramalho, K. M., Cunha, S. R., Gonçalves, F., Escudeiro, G. S., Steiner-Oliveria, C., Horliana, A. C. R. T., & Eduardo, C. de P. (2021). Photodynamic therapy and Acyclovir in the treatment of recurrent herpes labialis: A controlled randomized clinical trial. *Photodiagnosis and Photodynamic Therapy*, 33, 1-6.
- Raman, R., Patel, K. J., & Ranjan, K. (2021). COVID-19: Unmasking Emerging SARS-CoV-2 Variants, Vaccines and Therapeutic Strategies. *Biomolecules*, 11(7), 993.
- Ramires, M., Mattia, M. B., Tateno, R. Y., Palma, L. F., & Campos, L. (2021). A combination of phototherapy modalities for extensive lip lesions in a patient with SARS-CoV-2 infection. *Photodiagnosis and photodynamic therapy*, 33, 1-2.
- Teixeira, I. S., Leal, F. S., Tateno, R. Y., Palma, L. F., & Campos, L. (2021). Photobiomodulation therapy and antimicrobial photodynamic therapy for orofacial lesions in patients with COVID-19: A case series. *Photodiagnosis and photodynamic therapy*, 34, 102281.