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RESEARCH

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ANTIMICROBIAL EFFICACY OF PHOTODYNAMIC THERAPY ON THE TREATMENT OF ORAL CANDIDIASIS IN PEOPLE LIVING WITH HIV/AIDS

Eficácia antimicrobiana da terapia fotodinâmica no tratamento da candidíase oral em pessoas vivendo com HIV/Aids

Eficacia antimicrobiana de la terapia fotodinámica en el tratamiento de la candidiasis bucal en personas viviendo con VIH/Sida

*Article derived from the dissertation entitled "Evaluation of the clinical efficacy of the use of antimicrobial photodynamic therapy as an approach to the treatment of oral candidiasis in people living with HIV / AIDS", which was presented, in 2018, to the Graduate Program in HIV / Infection AIDS and Viral Hepatitis, Federal University of the State of Rio de Janeiro - UNIRIO.

Carlos Felipe Gomes Izoton[1], *Mônica Simões Israel*[2]

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ABSTRACT

Objective: evaluate the antimicrobial efficacy of photodynamic therapy in the treatment of oral candidiasis in people living with HIV/aids. **Method:** experimental, qualitative and descriptive study with 18 people living with HIV/aids who presented oral candidiasis, over 18 years of age, who were being treated at the Gaffrée and Guinle University Hospital. This group was subdivided into a control group, composed of seven people, who received treatment with photodynamic and antifungal therapy, and an experimental group, with 11, who received only the photodynamic therapy. The evolution of the treatment of each participant was followed by photographic registers in two appointments, initial and final. This research was approved by the Research Ethics Committee from the hospital, dictum number 2.431.107. **Results:** most of the participants showed clinical improvement, albeit discrete, and in only one there was clinical worsening. **Conclusion:** antimicrobial photodynamic therapy may be effective in the treatment of oral candidiasis in people living with HIV/aids.
Descriptors: Photodynamic therapy; Oral candidiasis; Opportunistic infections related to AIDS; Fungal drug resistance.

1 Dental surgeon, Master's student in the Postgraduate Program in HIV / AIDS and Viral Hepatitis Infection, Federal University of the State of Rio de Janeiro, Rio de Janeiro - RJ - Brazil.

2 Dental surgeon, PhD in Bucodental Pathology at Universidade Federal Fluminense, Adjunct Professor at the State University of Rio de Janeiro, Rio de Janeiro - RJ - Brazil.

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RESUMO

Objetivo: avaliar a eficácia antimicrobiana da terapia fotodinâmica no tratamento da candidíase oral em pessoas vivendo com HIV/aids. **Método:** estudo experimental, qualitativo e descritivo com 18 pessoas vivendo com HIV/aids que manifestavam a candidíase oral, maiores de 18 anos, que estavam em tratamento no Hospital Universitário Gaffrée e Guinle. Este grupo subdividiu-se em um grupo controle, composto por sete pessoas, que recebeu tratamento com a terapia fotodinâmica e antifúngicos, e um grupo experimental, com 11, que recebeu apenas a terapia fotodinâmica. A evolução do tratamento de cada participante foi acompanhada por registros fotográficos em duas consultas, inicial e final. Esta pesquisa foi aprovada pelo Comitê de Ética em Pesquisa do hospital, parecer número 2.431.107. **Resultados:** a maioria dos participantes apresentou melhora clínica, ainda que discreta, e em apenas um houve piora clínica. **Conclusão:** a terapia fotodinâmica antimicrobiana pode ser eficaz no tratamento da candidíase oral em pessoas vivendo com HIV/aids.

Descritores: Terapia fotodinâmica; Candidíase oral; Infecções oportunistas relacionadas com aids; Resistência fúngica a drogas.

RESUMEN

Objetivo: evaluar la eficacia antimicrobiana de la terapia fotodinámica en el tratamiento de la candidiasis bucal en personas que viven con VIH/sida. **Método:** estudio experimental, cualitativo y descriptivo con 18 personas viviendo con VIH/sida que manifestaban la candidiasis bucal, mayores de 18 años, que estaban en tratamiento en el Hospital Universitario Gaffrée y Guinle. Este grupo se subdividió en grupo control, compuesto por siete personas, que recibió tratamiento con la terapia fotodinámica y antifúngicos, y un grupo experimental, con 11, que recibió sólo la terapia fotodinámica. La evolución del tratamiento de cada participante fue acompañada por registros fotográficos en dos consultas, inicial y final. La investigación fue aprobada por el Comité de Ética en Investigación del lugar, dictamen número 2.431.107. **Resultados:** la mayoría de los participantes presentó mejoría clínica, aunque discreta, y en apenas uno hubo empeoramiento clínico. **Conclusión:** la terapia fotodinámica antimicrobiana puede ser eficaz en el tratamiento de la candidiasis bucal en personas que viven con el VIH/sida.

Descriptores: Terapia fotodinámica; Candidiasis bucal; Infecciones oportunistas relacionadas con el sida; Resistencia fúngica a las drogas.

INTRODUCTION

Oral candidiasis is the most prevalent oral lesion in people living with HIV / AIDS (PLWHA), especially those who have not yet started antiretroviral therapy (ART)[1], in which the pseudomembranous variant of this disease is most commonly diagnosed[2]. Regular distribution of ART promoted a significant improvement in the health status of PLWHA[3], however, the occurrence of oral candidiasis in PLWHA under ART is not uncommon[4]. Clinical manifestation is caused by a reduction in T Lymphocyte + CD4 count (LTCD4 +), less than 200 cells/μℓ, and an increase in HIV viral load (CV), greater than 3000 copies/mℓ[5]. Conventional treatment of oral candidiasis is based on the use of topical (e.g. nystatin) and systemic (e.g. fluconazole)[6] antifungal drugs, however, there are limitations: they cause side effects, favor antifungal resistance when used for a long time or repeatedly and do not prevent recurrence of the injury in the short term[7].

The use of photodynamic therapy (PDT) as an antimicrobial therapeutic strategy has been widely studied in the last decade. Basically, PDT consists in associating a light source and a photosensitizing dye compatible with this light, applying them to a tissue that has oxygen to promote the death by photooxidation of pathogenic microorganisms – among them the fungi[8].

This technique has shown to be promising in reducing *C. albicans* colonies in *in vitro*[9-11] and *in vivo*[12,13] assays. PDT was also effective in the treatment of oral candidiasis in PLWHA, without causing side effects, both isolated[14] and when associated with topical antifungals[15]. Thereby, the aim of this paper was to show the antimicrobial efficacy of PDT in the treatment of oral candidiasis in PLWHA.

METHODOLOGY

A methodological course of an experimental research was performed, qualitative and descriptive, with PLWHA, with clinical signs and symptoms of oral candidiasis, over 18 years old, which were being treated in the wards and ambulatories of the Gaffrée and Guinle University Hospital (HUGG). Patients using removable oral prostheses, smokers, pregnant women, skin cancer in the region, glaucoma and cataract patients without medical supervision were not included in the evaluations. This research was submitted to the HUGG Research Ethics Committee of the Federal University of Rio de Janeiro and approved under dictum number 2.431.107, and all participants were voluntarily invited to participate after signing an informed consent form (ICF), notifying them of the risks and benefits of it prior to their enrollment.

Participants were separated into two groups (CG, control group and EG, experimental group), which received different treatments. In the CG group, 14 days of conventional antifungal therapy was used (fluconazole, nystatin, ketoconazole, etc.), associated with PDT, mediated by *Therapy* EC diode laser (red λ=660nm, power 100mW ± 20%; and infrared λ=808nm, 100mW power ± 20%; DMC manufacturer; São Carlos manufacturing site, SP - Brazil), nine joules energy, 90 seconds exposure time; with 0.01% methylene blue; with pre-irradiation time of four minutes; and with a single irradiation at the injury site. The EG was submitted only to PDT, in the same parameters used in the CG.

The evolution of the treatment was followed, from a qualitative methodological approach, in two moments: the first for the collection of information from the medical records, evaluation and clinical diagnosis of oral candidiasis, prescription of the proposed therapy for each group and oral hygiene instruction (OHI), called "D0" (day zero); and the second for clinical control after 14 days, called "D14" (day 14), in which the clinical evaluation, photographic records, reports of patients' perceptions of each treatment used and the OHI were repeated.

Each participant was randomly and sequentially numbered, being the first numbered 001 and the last 030. Photographs of oral Candida ("before and after") lesions of

each participant were scored (absent = 0, mild = 1, moderate = 2 and severe = 3), and also marked with signs, so to evaluate if the suggested treatment provided improvement (+), worsening (-) or there was no difference (0).

RESULTS

During this research, 30 participants were evaluated, but 12 were excluded because they did not return during the period stipulated by the researcher, totaling 18 (100%) participants, seven (38,89%) participants in the CG (007, 015, 016, 018 , 024, 028 and 030) and the other 11 participants in the GE (003, 006, 009, 011, 013, 014, 022, 023, 026, 027 and 029). Of these, 16 (88,89%) were on ART treatment, while only two (11,11%) were without ART.

In the CG, four (57,14%) participants (007, 016, 018 and 030) showed, in the initial photograph ("before") taken at the first consultation (D0), clinical signs of oral candidiasis classified as severe, while the other three (42,86%) (015, 024, 028) had moderate clinical signs. On the 14th day (D14), after photographic evaluation, the total absence of clinical signs was verified in two (28,57%) participants (015 and 030); clinical improvement from moderate to mild in two (28,57%) (024 and 028); from severe to mild in one (14,29%) (018); and in two (28,57%) (007 and 016) there was a slight clinical improvement, but the severe classification was maintained (see **Tables 1 and 2**).

Table 1 - Signal classification of participants in the control group (CG) regarding the success / failure of the therapy used (Antifungal + PDT) after 14 days..

Participants	Score D0	Score D14	Signs
007	3	3	0
015	2	0	+
016	3	3	0
018	3	1	+
024	2	1	+
028	2	1	+
030	3	0	+

Elaborated by the author

Table 2 - Percentage of improvement, worsening or no difference in CG treatment after 14 days.

Qualitative	Participants	Percentage
Improvement	5	71,43%
Worsening	0	0,00%
No difference	2	28,57%
Total	7	100,00%

Elaborated by the author

In the EG, seven (54,54%) participants (003, 009, 013, 014, 022 and 026) showed, in the initial photograph, moderate clinical signs of oral candidiasis on D0; and five (45,46%) (006,011,023,027,029) received the classification of mild oral candidiasis. In D14, after photographic evaluation, it was observed that: the total absence of clinical signs of the disease (mild to absent) in two (18,18%) participants (006 and 011); clinical improvement from moderate to mild in 6 six (54,54%) (003, 009, 013, 014, 022, and 026); clinical worsening from mild to moderate in one (9,09%) (029); and in two (18,18%) (023 and 027), no clinically significant differences were observed (see **Tables 3 and 4**).

The clinical worsening of 029 was attributed to his long hospitalization, intubation and ventilatory assistance. Even in participants who did not change the oral candidiasis lesion classification after 14 days (023 and 027), a slight clinical improvement was observed.

Table 3 - Signal classification of participants in the experimental group (EG) regarding the success/failure of the therapy used (PDT) after 14 days.

Participants	Score D0	Score D14	Signs
003	2	1	+
006	1	0	+
009	2	1	+
011	1	0	+
013	2	1	+
014	2	1	+
022	2	1	+
023	1	1	0
026	2	1	+
027	1	1	0
029	1	2	-

Elaborated by the author

Table 4 - Percentage of improvement, worsening or no difference in EG treatment after 14 days.

Qualitative	Participants	Percentage
Improvement	8	72,73%
Worsening	1	9,09%
No difference	2	18,18%
Total	11	100,00%

Elaborated by the author

The non-parametric *Wilcoxon-Mann-Whitney* test was applied to statistically compare the difference in the proposed treatments for CG and EG. However, there was

not enough statistical scientificity to determine in which group the treatment was better, due to the small number of participants (18) evaluated and the asymmetric number of participants in each group (CG = 7 and GE = 11).

DISCUSSION

Oral candidiasis is a very common oral lesion in PVHA[1]. The pseudomembranous form of this disease is frequently diagnosed in PLWHA who have not yet started ART[2] and was observed in this research, precisely in two participants (024 and 028) who had not yet chosen this therapy. Even with ART reducing the occurrence of opportunistic infections and promoting a significant improvement in the general health of PLWHA[3], it does not exempt them from manifesting oral candidiasis[4], as it was observed in 16 (88,89%) participants in this experiment who were under ART. Conventional antifungal therapies, responsible for the treatment of oral candidiasis, do not always achieve efficacy in the expected time and do not prevent recurrence of short-term lesions[8,9]. These findings were confirmed in this experiment, in which all participants manifested oral candidiasis, even those using antifungals. An experimental study with 21 PLWHA showed that fluconazole did not prevent recurrence of oral candidiasis when they were reevaluated within 30 days, whereas in patients receiving PDT, there was no recurrence of the lesion during the same reevaluation period[14]. The combination of PDT and fluconazole was effective in reducing *C. albicans* colonies in *in vitro*[10,11] and *in vivo*[12,13] studies. In this study, participants 015 and 018, respectively, received PDT/nystatin and PDT/fluconazole exhibited a reduction in oral candidiasis severity ratings when reassessed after 14 days.

CONCLUSION

This research reinforces the importance of the need to adopt an adjunctive therapeutic strategy to the conventional treatment of oral candidiasis in PLWHA. In this regard, PDT can play such a supporting role by reducing the prevalence of the disease and its clinical course, as well as decreasing antimicrobial resistance to antifungals. Therefore, PDT can contribute to the improvement of the patient's general health.

The results of this research indicated that in only one patient, who received PDT alone (GE), there was a clinical worsening of oral candidiasis. However, this worsening cannot be attributed to the experiment, because this patient went through a long period of intubation and ventilatory assistance, and this condition contributes to Candida infection. In all other patients in both groups there was improvement, slight improvement or no clinically significant differences. In light of this, it has been concluded that PDT, combined with red laser and 0.01% methylene blue laser, can be considered a promising and safe strategy in the treatment of oral candidiasis in PLWHA.

Synergism between PDT and conventional antifungal drugs may increase the efficacy of these drugs, reducing relapse and reducing the time course of the disease. This association can positively impact a shorter hospitalization time for the patient and, consequently, a decrease in expenses with this patient in health services.

There was no statistical significance in determining which group (CG or EG) had the most effective treatment due to the small number of participants. For this same reason, it was not possible to evaluate whether the use of PDT alone, as the only therapeutic strategy in the treatment of oral candidiasis in PLWHA, can exhibit the same results already established as traditional antifungal therapy. These questions reaffirm the need for further research on the same theme.

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Corresponding author
Carlos Felipe Gomes Izoton
Address: Rua General Silveira Sobrinho, 416 Apto. 303
Rio de Janeiro/RJ, Brazil
Zip code: 21221-290
E-mail address: ffelipeizoton@hotmail.com
Telephone number: +55 (21) 99793-0208

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