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ORIGINAL ARTICLE

The efficacy of photodynamic therapy for herpes simplex lesions in immunocompetent and oncologic individuals

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Abstract:

Aims: To investigate the efficacy of antibacterial photodynamic therapy (APDT) for the treatment of herpes simplex oral and perioral lesions in immunocompetent and oncologic individuals. **Methods and Results:** APDT was applied in G1 (immunocompetent, n=26) and G3 (oncologic, n=6) with methylene blue 0.01% followed by 660ηm low level LASER in all the lesion area. In G2, immunocompetent patients received Acyclovir cream 50mg/g prescription. Lesion stage, size, edema, and pain degree were obtained at the beginning of the treatment (T0), after 24 hours (T1), 48 hours (T2), 72 hours (T3), and 7 days (T4). Intra-group analyses showed significant improvement in all criteria for G1 and G3 between T0 and T4 ($p<0.05$), while for G2 no differences were found in lesion stage and pain level between study times ($p>0.05$). Most of G1 individuals showed crust stage in T2 and T3, while most of G3 individuals presented papule or vesicle at the same times ($p<0.05$); and G2 presented higher scores of edema in T2 than G1 and G3 at the same time ($p<0.05$). **Conclusions:** It is possible to conclude that APDT is an effective adjuvant treatment for HSV oral and perioral infections in both immunocompetent and oncologic individuals.

Keywords: Herpes Simplex; Photochemotherapy; Hematologic Neoplasms.

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INTRODUCTION

The herpes virus family included double-stranded DNA viruses, from which the most commonly associated with oral and perioral lesions is the herpes simplex virus 1 (HSV-1)[1]. HSV-1 infections are primary acquired at the mucosal surfaces and then the HSV establish a latent life-long relationship with their human host[2]. Recurrent oral and perioral herpes lesions affect approximately 67% of the world's population under the age of 50 years[3]. In immunocompetent patients, HSV recurrences causing perioral and oral lesions are commonly associated with several factors, including temporary immunosuppression stages, and rarely cause more severe consequences than the local discomfort and aesthetic impairment of the lesions[1]. However, neutropenic cancer individuals have higher rates of HSV reactivation (approximately 50%)[4]. In addition, the HSV-1 oral reactivations in neutropenic cancer patients, such as the ones with hematological malignancies, may result in increased morbidity and was associated with worse survival and poor prognosis[5].

The most common treatment for HSV-1 infections is anti-viral drugs, such as acyclovir or valacyclovir[6]. Several studies reported that in patients undergoing chemotherapy the systemic prophylaxis with anti-viral therapy also has the capability of reducing recurrence frequency and, consequently, reducing morbidity and improving prognosis[7]. Despite the benefits of conventional antiviral therapy for HSV-1 infections, there are studies indicating that the prolonged administration of these drugs may lead to the development of acyclovir-resistant HSV[8,9]. Although resistance to acyclovir presents a low prevalence in immunocompetent individuals (≤1%)[8], rates for immunocompromised hosts are much higher (4–10%)[9], which include patients with hematological malignancies undergoing chemotherapy. Considering the consequences of HSV infections and the possibility of drug resistance in these viruses in oncologic patients, the use of alternative therapies for HSV may be the key to the management and control of HSV infections in these patients.

The antimicrobial photodynamic therapy (APDT) emerges as an alternative for conventional anti-viral treatments for oral and perioral herpetic lesions[10]. The APDT demands three essential elements: (1) photosensitizers; (2) source of light; (3) oxygen dissolved in the treated tissue[11]. The efficacy of the APDT relies on the activation of the photosensitizer by the source of light that causes the transformation of molecular oxygen into reactive oxygen species (ROS), which cause the cytotoxic effect on the infected cells[12,13]. One of the most significant benefits of the therapy that it seems to be effective for both multi-drug resistant and native microbes[11]. In addition, evidence indicates that APDT effects seem much faster than other anti-microbial therapies and no case of resistance to APDT was reported until date[11].

Until date, four clinical cases and two clinical trials reporting the treatment of oral herpetic lesions in oncologic patients with APDT were published, which showed that the treatment was effective for herpetic oral lesions[14-17]. Current evidence points out that APDT may be an efficacy alternative for the treatment of herpetic oral and perioral lesions in immunocompetent and oncologic individuals[10,14,15]. However, the evidence for oncologic patients is still limited and to the best of the authors' knowledge, there is no clinical study on the efficacy of APDT for herpes simplex lesions comparing results for immunocompetent and oncologic individuals. Therefore, the aim of this study was to investigate the efficacy of APDT for the treatment of oral and perioral herpetic lesions in oncologic and immunocompetent individuals.

MATERIAL AND METHODS

Study design and ethical approval

The present non-randomized clinical study was performed at the Professor Polydoro Ernani de São Thiago University Hospital, Federal University of Santa Catarina, Brazil. The participants were selected from September 2015 to September 2018 based on convenience. The study was approved by the Ethics Committee in Human Research of the authors' institution (statement number: 1.231.409), all participants signed a consent form previous to the beginning of the intervention, and their identity remained anonymous according to the Declaration of Helsinki.

Sample

Al patients presented oral or perioral herpetic lesions. It is worth emphasizing that herpes diagnosis was based solely on clinical observations. Three groups composed this study sample: (G1) Group 1, immunocompetent volunteer participants which received APDT; (G2) Group 2, immunocompetent volunteer participants which received treatment with topical acyclovir; and (G3) Group 3, participants with hematological malignant who received adjuvant treatment with APDT.

Inclusion criteria included participants with a minimum of 18 years of age who voluntarily collaborated with the protocol of treatment. Patients were excluded in cases of signs of herpes zoster infection, primary herpetic lesions or that have received some anti-viral therapy for the present lesion before the begging of the study. Also, for G1 and G2 the patients were excluded in case of the presence of any condition that caused prolonged immunosuppression or if they were using some immunosuppressant medication. In addition, participants from G3 were individuals affected by leukemia, lymphoma, or other hematological malignancies who were receiving antineoplastic treatment (chemotherapy). It is important to emphasize that, due to the immunosuppression caused by the antineoplastic treatment, participants from G3 received prophylactic treatment with systemic acyclovir (400mg, 12/12 hours) accordantly to the medical protocol established at the hospital. Therefore, due to the ethical limitation, this systemic therapy was not suspended.

Treatment protocol

All participants attended the hospital five times in seven days: (T0) first contact, and begging of treatment; (T1) 24 hours after T0; (T2) 48 hours after T0; (T3) 72 hours after T0; (T4) control of lesion evolution, 7 days after T0.

Treatment with APDT (G1 and G3) was performed by a habilitated and calibrated professional (Figure 1). Lesions in the vesicle stage (Figure 1a) were perforated with a sterilized needle (Figure 1b), and the liquid content was drained with sterile gauze with caution aiming to avoid spreading the fluid to adjacent areas (Figure 1c). A small swab soaked in 0.01% methylene blue aqueous solution was applied on the lesion (Figure 1d), and, after 5 min, the excess dye was removed (pre-irradiation period) (Figure 1e). Then, lesions were irradiated point to point equally divided with 1 cm between them, with a 660-nm low-power laser (Laser Therapy XT; DMC®, São Carlos, Brazil) (Figure 1f). The laser parameters were: 660 nm wavelength, spot size of 0.028 cm^2, continuous mode, 100mW power, energy dosage 4J/cm^2, and 40 seconds of application per point. The applications were repeated daily until T3, the formation of crust, or the disappearance of intraoral lesions. It is worth mentioning that, even if the lesions evolved to crust or cure the participants attended the hospital at the set dates for clinical evaluation and control

Treatment with topical acyclovir (G2) was prescribed as follows: 50mg/g cream acyclovir for topical application covering all lesion's extension five times a day until lesion disappearance. Participants were responsible for the application, and they attended the hospital at the previously mentioned times for clinical evaluation and control.

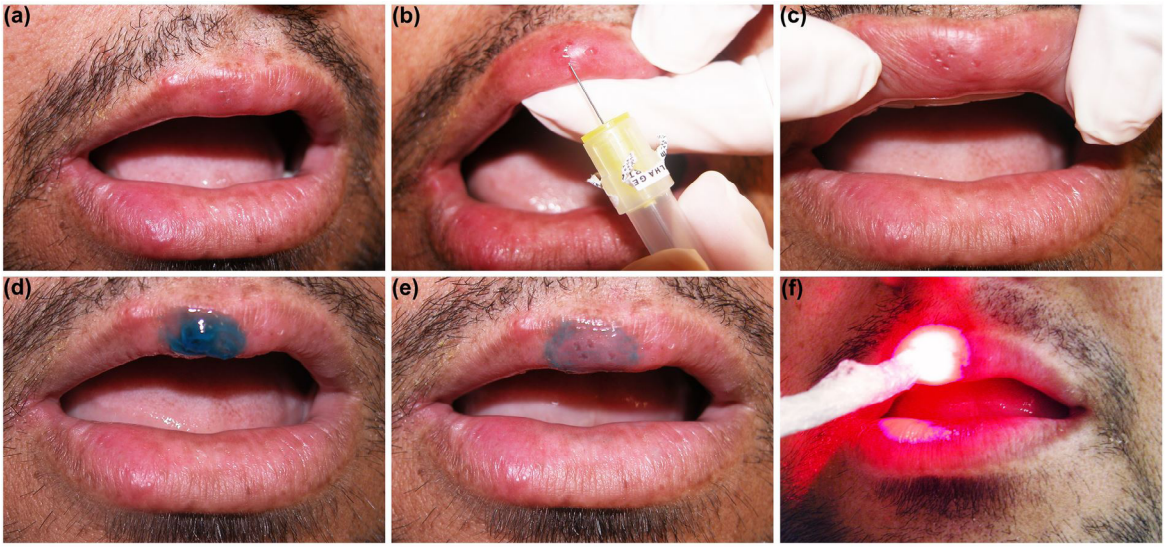

Figure 1. Methodology of APDT application. (a) Initial lesion in vesicle stage; (b) Perforation of the vesicle with a sterilized needle; (c) Visual aspect after vesicle perforation and liquid content drainage; (d) Application of 0.01% methylene blue aqueous solution on the lesion; (e) Visual aspect after 5 min of 0.01% methylene blue aqueous solution application and removal of the excess; (f) Irradiation of the lesion with 660-nm low-power laser (Laser Therapy XT; DMC®, São Carlos, Brazil).

Data collection

All participant received an initial anamneses, in which the following items were registered: age, sex, marital status, skin color, tobacco and alcohol consumption habits, comorbidities, medicines used, duration of herpes simplex infection, frequency of recurrence, approximated duration of the episodes, preferential location of lesions, and previously used therapies. For patients in G3 data on underlying disease, chemotherapy protocol, and time of hospitalization were also collected.

For all participants data in regards to herpes simplex lesions were collected in all study times by a calibrated researcher with methodology adapted from De Carvalho *et al.* (2010)[16]. Lesion stages were scored as 0 for prodromic, 1 for macula or erythema, 2 for papule, 3 for vesicles, 4 for crust, and 5 for total healing. Lesion size was assessed based on the larger diameter and scored as 0 for absent, 1 for small (from 0.1 to 2.0 mm), 2 for medium (2.1 – 4.9 mm), and 3 for large (more than 5.0 mm). The presence of edema was classified as 0 for absent, 1 for discrete swelling, 2 for moderate swelling, and 3 for large swelling (covering a perimeter of more than 1cm). In addition, the intensity of pain was assessed with a visual analog scale and score from 0 to 10.

Statistical analysis

Data were analyzed using the software SPSS Statistics 25 (IBM Corp., Armonk, NY, USA). Firstly, the Shapiro-Wilk test was conducted to assess the normality distribution of the residuals. Results showed that the data did not fit a normal distribution. The non-parametric Kruskal-Wallis test was performed to compare the results between the three groups (intergroup analyzes). For intragroup analyzes, the non-parametric Friedman test for paired data was performed. The statistical significance was set at α=0.05.

RESULTS

The sample was constituted by 36 participants, of which 26 composed G1, four G2, and six G3. The majority of participants from G1 and G2 were female, while participants from G3 were predominant males. In regards to skin color, the majority of patients from all groups were fair-skinned. The preferred location of the lesions was extraoral, being 15 cases (42%) in upper lip and 12 cases (36%) in the lower lip. In addition, four patients from G1 and five patients from G3 presented intraoral herpes simplex lesions (Table 1). The majority of patients reported the first infection in childhood (61%), with recurrence rates ranging from one to 12 times a year and 7 to 15 days of duration. 72% of patients reported previous treatment with topical or systemic acyclovir. Furthermore, participants with acute lymphoid leukemia (n=3), acute myeloid leukemia (n=2), and Burkitt's lymphoma (n=1) composed G3. The chemotherapy regimen more commonly reported was Hyper CVAD and other regimens with cytarabine.

In regards to lesion stage evolution, intragroup analysis showed statistically significant differences in G1 between T0 and all other times of research. Intragroup analyses for G3 showed statistically significant difference between T0 and T4. No statistical significances were found in intragroup analysis of G2. In addition, intergroup analyses regarding lesion stage showed statistically significant differences between G1 and G3 in T2 and T3. G1 patients in T2 and T3 more commonly presented lesions in crust stage, while the majority of G3 patients had not reached crust stage at the same times

Table 1. General characteristics of participants.

		G1 (n=26)		G2 (n=4)		G3 (n=6)		Total (n=36)	
		n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Gender	*Male*	5	19.2	1	25	5	83.3	11	30.6
	Female	21	80.8	3	75	1	16.7	25	69.4
Skin-color	*Fair-skinned*	20	76.9	3	75	4	66.7	27	75
	Other	6	23.1	1	25	2	33.3	9	25
Smoker	*Yes*	4	15.4	0	-	0	-	4	11.1
	No	22	84.6	4	100	6	100	32	88.9
Drinker	*Yes*	2	7.7	0	-	0	-	2	5.5
	No	24	92.3	4	100	6	100	34	94.5
Lesion location	*Intraoral*	4	15.4	0	-	5	83.3	9	25
	Extraoral	22	84.6	4	100	1	16.7	27	75

Legend: G1, immunocompetent individuals treated with antimicrobial photodynamic therapy; G2, immunocompetent individuals treated with topical acyclovir; G3, oncologic patients treated with antimicrobial photodynamic therapy; n, number.

(Table 2). In figures 2, 3, and 4 are representative images of the evolution of G1, G2, and G3 cases, respectively.

Results from intragroup analysis regarding lesion size showed significant differences in G1 between T0 and T2, T3, and T4. Lesion size intragroup analysis for G2 revealed significant differences between T0 and T4. For G3, lesion size in T0 was significantly larger than in T3 and T4. No statistical differences were found in the intergroup analyses (Table 3).

Intragroup analysis for edema for G1 revealed statistical differences between T0 and all the other timer of study. In regards to edema for G2 and G3 T0 was only statistically different from T4. Results from inter-group analysis showed a statistical difference in T2, post-hoc analysis revealed statistical differences between G1 and G2, and between G2 and G3 in this time of the study. It is important to emphasize that the majority of G1 and G3 patients presented absence of edema in T2, while G2 patients presented in their majority moderate to large swelling at the same time (Table 4).

Considering pain level, intragroup analysis for G1 showed statistical differences between T0 and T2, T3, and T4. No statistical differences were found in intragroup analysis of pain level for G2. For G3, pain level at T0 was significantly higher than in T4. Intergroup analyses of pain level showed no statistical difference between study groups (Table 5).

DISCUSSION

In the last decades, several studies have focused on the control of opportunistic infections in oncologic patients, such as HSV recurrence[7,15,19-23]. The control of these infections may result in the improvement of prognosis and quality of life of oncologic patients undergoing chemotherapy[5]. APDT seems a useful adjuvant therapy for HSV recurrence, especially in oncologic patients who show more severe consequence of HSV lesions and are reported to have higher rates of acyclovir-resistant HSV infections[8,9]. Therefore, this clinical study aimed to investigate the efficacy of APDT for both immunocompetent and oncologic patient, to compare the responses of both groups to the APDT, and to compare the results of APDT with a group treated with topic acyclovir.

In the present study, the treatment of oral and perioral herpetic lesion in immunocompetent and oncologic individuals resulted in an improvement in all criteria analyzed (lesion stage, lesion size, edema, and pain), which indicates that this treatment is effective

Table 2. Results of lesion stage evolution for different treatment groups†.

Score	INITIAL (T0)						24 HOURS (T1)						48 HOURS* (T2)						72 HOURS* (T3)						7 DAYS (T4)					
	G1[a]		G2[e]		G3[f]		G1[b]		G2[e]		G3[fg]		G1*[bc]		G2[e]		G3*[fg]		G1*[cd]		G2[e]		G3*[fg]		G1[d]		G2[e]		G3[g]	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-
1	0	-	0	-	0	-	0	-	0	-	0	-	1	3.9	0	-	0	-	1	3.9	0	-	1	16.7	0	-	0	-	0	-
2	5	19.2	2	50	3	50	6	23.1	0	-	2	33.3	2	7.7	0	-	2	33.3	1	3.9	0	-	2	33.3	0	-	0	-	1	16.7
3	20	76.9	2	50	2	33.3	5	19.2	3	75	2	33.3	0	-	2	50	2	33.3	0	-	1	25	1	16.7	0	-	0	-	0	-
4	1	3.9	0	-	1	16.7	15	57.7	1	25	2	33.3	23	88.4	2	50	2	33.3	23	88.4	2	75	2	33.3	17	65.4	4	100	1	16.7
5	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	3.9	0	-	0	-	9	34.6	0	-	4	66.6

Legend: (†) Results from Friedman statistical test showed statistical significant differences in lesion phase in G1 ($p<0.0001$), G2 ($p=0.036$), and Oncology ($p=0.014$) groups between times. Equal superscript letters represent no significant differences in the pair-wise comparison in the same treatment group ($p>0.05$). Different superscript letters represent significant differences in the pair-wise comparison in the same treatment group ($p<0.05$). (*) Kruskal-Wallis tests revealed statistical significant differences between groups in 48 and 72 hours ($p<0.05$), post-hoc analyses revealed statistical significant difference in Dunn-Bonferroni's pair-wise comparison between G1 and G3 in 48 hours ($p=0.030$) and in 72 hours ($p=0.006$). G1, immunocompetent individuals treated with antimicrobial photodynamic therapy; G2, immunocompetent individuals treated with topical acyclovir; G3, oncologic patients treated with antimicrobial photodynamic therapy; n, number.

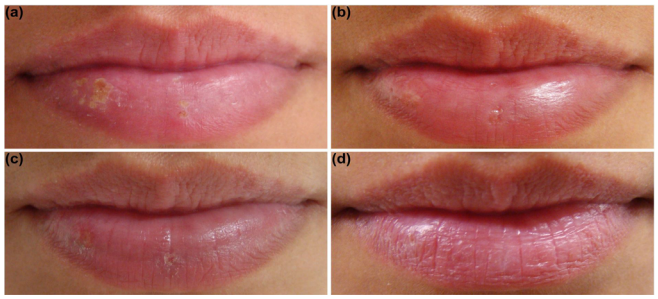

Figure 2. Representation of G1 clinical evolution. (a) Initial lesion in vesicle stage; (b) 24 hours after the first APDT application (T1); (c) 72 hours after the first APDT application (T3); (d) 7 days after the first APDT application (T4).

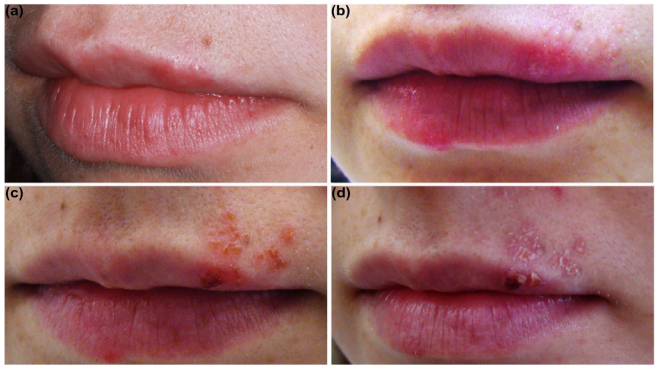

Figure 3. Representation of G2 clinical evolution. (a) Initial lesion in vesicle stage; (b) 24 hours after the begging of acyclovir application (T1); (c) 72 hours after the begging of acyclovir application (T3); (d) 7 days after the begging of acyclovir application (T4).

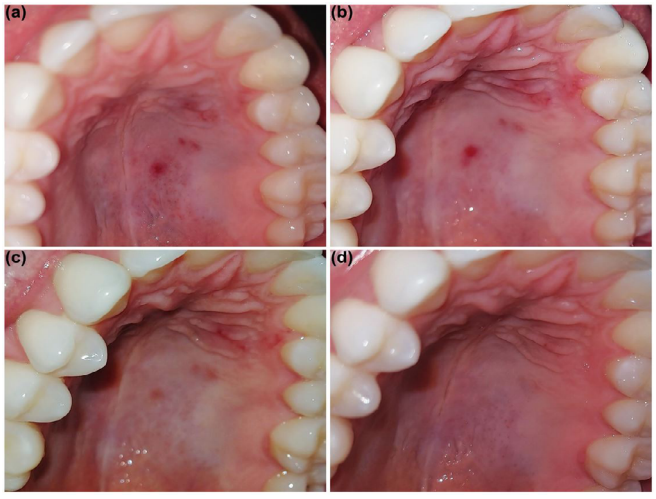

Figure 4. Representation of G3 clinical evolution. (a) Initial lesion in ulcer stage; (b) 24 hours after the begging of APDT application (T1); (c) 72 hours after the begging of APDT application (T3); (d) 7 days after the begging of APDT application (T4).

for HSV lesions. These results corroborate with results from previous studies investigating the efficacy of APDT for HSV oral and perioral lesions, which suggested that APDT could be useful for treatment of HSV

Table 3. Results of lesion size for different treatment groups[†].

Score	INITIAL (T0)						24 HOURS (T1)						48 HOURS (T2)						72 HOURS (T3)						7 DAYS (T4)					
	G1[a]		G2[c]		G3[b]		G1[ab]		G2[c]		G3[b]		G1[bc]		G2[ef]		G3[hi]		G1[c]		G2[ef]		G3[ij]		G1[d]		G2[g]		G3[j]	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	*n*	%	*n*	%	*n*	%
0	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	3.9	0	-	1	16.7	9	34.6	1	25	5	83.3
1	1	3.9	1	25	1	16.7	7	26.9	0	-	1	16.7	8	30.8	1	25	2	33.3	15	57.7	2	50	3	50	15	57.7	3	75	1	16.7
2	15	57.7	1	25	2	33.3	10	38.5	2	50	2	33.3	16	61.5	2	50	3	50	8	30.8	2	50	1	16.7	2	7.7	0	-	0	-
3	3	11.6	2	50	3	50	9	34.6	2	50	3	50	2	7.7	1	25	1	16.7	2	7.7	0	-	1	16.7	0	-	0	-	0	-

Legend: (†) Results from Friedman statistical test showed statistical significant differences in lesion size in G1 (p<0.0001), G2 (p=0.044), and Oncology (p<0.0001) groups between times. Equal superscript letters represent no significant differences in the pair-wise comparison in the same treatment group (p>0.05). Different superscript letters represent significant differences in the pair-wise comparison in the same treatment group (p<0.05). G1, immunocompetent individuals treated with antimicrobial photodynamic therapy; G2, immunocompetent individuals treated with topical acyclovir; G3, oncologic patients treated with antimicrobial photodynamic therapy; n, number.

Table 4. Results of edema for different treatment groups†.

Score	INITIAL (T0)						24 HOURS (T1)						48 HOURS* (T2)						72 HOURS (T3)						7 DAYS (T4)					
	G1[a]		G2[d]		G3[f]		G1[b]		G2[d]		G3[fg]		G1*[c]		G2*[de]**		G3**[fg]		G1[c]		G2[de]		G3[fg]		G1[c]		G2[e]		G3[g]	
	n	*%*	*n*	*%*	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	*n*	*%*	*n*	*%*	*n*	*%*
0	2	7.7	0	-	2	33.3	8	30.8	0	-	3	50	14	53.8	0	-	4	66.6	18	69.2	2	50	5	83.3	25	96.1	3	75	6	100
1	10	38.5	2	50	2	33.3	10	38.5	1	25	2	33.3	10	38.5	1	25	1	16.7	8	30.8	1	25	1	16.7	1	3.9	1	25	0	-
2	9	34.6	2	50	2	33.3	5	19.2	1	25	1	16.7	2	7.7	1	25	1	16.7	0	-	0	-	0	-	0	-	0	-	0	-
3	5	19.2	0	-	0	-	3	11.5	2	50	0	-	0	-	2	50	0	-	0	-	1	25	0	-	0	-	0	-	0	-

Legend: (†) Results from Friedman statistical test showed statistical significant differences in edema in G1 (p<0.001), G2 (p=0.025), and Oncology (p=0.016) groups between times. Equal superscript letters represent no significant differences in the pair-wise comparison in the same treatment group (p>0.05). Different superscript letters represent significant differences in the pair-wise comparison in the same treatment group (p<0.05). (*) Kruskal-Wallis tests revealed statistical significant differences between groups in 48 (p<0.05), post-hoc analyses revealed statistical significant difference in Dunn-Bonferroni's pair-wise comparison between G1 and G2 (p=0.012), and G2 and G3 (p=0.028) in 48 hours. G1, immunocompetent individuals treated with antimicrobial photodynamic therapy; G2, immunocompetent individuals treated with topical acyclovir; G3, oncologic patients treated with antimicrobial photodynamic therapy; n, number.

Table 5. Results of pain level for different treatment groups†.

Score	INITIAL (T0)						24 HOURS (T1)						48 HOURS (T2)						72 HOURS (T3)						7 DAYS (T4)					
	G1[a]		G2[e]		G3[f]		G1[ab]		G2[e]		G3[f]		G1[bc]		G2[e]		G3[f]		G1[cd]		G2[e]		G3[fg]		G1[d]		G2[e]		G3[g]	
		%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	5	19.2	0	-	2	33.3	12	46.2	1	25	1	16.7	15	57.7	1	25	1	16.7	19	73.1	2	50	3	50	24	92.3	3	75	6	100
1	5	19.2	1	25	1	16.7	5	19.2	0	-	3	50	4	15.4	0	-	3	50	4	15.4	1	25	3	50	2	7.7	1	25	0	-
2	4	15.4	2	50	1	16.7	1	3.9	0	-	0	-	4	15.4	1	25	2	33.3	1	3.9	0	-	0	-	0	-	0	-	0	-
3	5	19.2	0	-	0	-	3	11.5	2	50	0	-	2	7.7	0	-	0	-	1	3.9	1	25	0	-	0	-	0	-	0	-
4	2	7.7	0	-	0	-	3	11.5	0	-	1	16.7	0	-	1	25	0	-	0	-	0	-	0	-	0	-	0	-	0	-
5	3	11.5	1	25	2	33.3	1	3.9	0	-	0	-	1	3.9	1	25	0	-	1	3.9	0	-	0	-	0	-	0	-	0	-
6	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-
7	1	3.9	0	-	0	-	0	-	1	25	1	16.7	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-
8	1	3.9	0	-	0	-	1	3.9	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-

Legend: (†) Results from Friedman statistical test showed statistical significant differences in pain level in G1 (p<0.0001) and Oncology (p=0.006) groups between times. No statistical significant differences were found in pain level in G2 between times. Equal superscript letters represent no significant differences in the pair-wise comparison in the same treatment group (p>0.05). Different superscript letters represent significant differences in the pair-wise comparison in the same treatment group (p<0.05). G1, immunocompetent individuals treated with antimicrobial photodynamic therapy; G2, immunocompetent individuals treated with topical acyclovir; G3, oncologic patients treated with antimicrobial photodynamic therapy; n, number.

recurrence in both oncological and immunocompetent individuals[10,15-17,24-26]. However, no clinical studies investigating and comparing the peculiarities of APDT in both immunocompetent and oncologic individuals was published until date. Therefore, future clinical studies are needed for a more definitive conclusion on this topic.

It is worth mentioning that for most criteria the HSV lesions' evolution was slower in oncologic than in immunocompetent individuals treated with APDT. In addition, a significant difference was found between G1 and G3 in both T2 and T3 in regards to lesion stage. Most oncologic individuals reached crust or cure stages only after seven days of follow-up, while most of immunocompetent individuals reached crust stage after 24 hours of treatment. On the other hand, the vast majority of oncologic individuals presented intraoral lesions, which, added up to their neutropenia, might also have influenced their response to the therapy[27]. These results suggest that APDT is efficient for the treatment of herpes simplex lesions in both immunocompetent and oncologic patients; however, the response in immunocompetent individuals is faster than in oncologic ones.

Patients with impaired immunity, such as the ones undergoing chemotherapy, are more susceptible to certain infections, which include HSV infections[28]. Therefore, usually, these patients receive prophylaxis with anti-viral drugs aiming the prevention of recurrence[19,21]. Even receiving antiviral prophylaxis approximately 7% of patients experience recurrence during chemotherapy[23]. Herpes infections in oncologic patients can present atypical manifestation and, usually, affect intraoral sites (*e.g.*, hard palate, inserted gingiva, and tongue dorsum)[22], which was also found in the present study. However, these infections in oncologic patients, especially the ones with hematological malignancies, can present severe systemic consequences[20], which highlights the importance of studying adjuvant therapies, such as APDT, aiming the improvement of therapy and the better understanding of differences in the response of immunocompetent and oncologic individuals.

It is important to emphasize that most available evidence on APDT efficacy for HSV lesions rely in case reports and, therefore, the finding from the present clinical study might contribute to a better understanding of the efficacy of APDT for HSV oral and perioral lesions as well as of the differences between the response from immunocompetent and oncologic individuals. These data might aid healthcare professionals to establish more personalized treatment protocols for HSV lesions in daily practice. As previously mentioned all oncologic individuals were receiving acyclovir prophylaxis according to international guidelines[19,21] and, even so, they developed HSV lesions, which indicates that the use of adjuvant treatments, such as APDT, might be essential for the better management of these infections in oncologic neutropenic patients. In addition, it is worth mentioning that APDT has no reported side effects for HSV treatment, it is faster than other antimicrobial agents, present a local effect, and can reduced frequency of HSV recurrence[11,15,24].

In the present study, the treatment of APDT presented better results than the treatment with topical acyclovir, especially in regards to edema. Although acyclovir is one of the most commonly used anti-viral for the treatment of HSV infections, the higher rates of acyclovir-resistant infections in oncologic patients require the use of alternative therapies in case of recurrences[7,9]. In this way, the results of the present study indicate that APDT might be superior to topical acyclovir in cases of HSV recurrences, however, in oncologic patients the use of systemic anti-viral prophylaxis is essential for the prevention of HSV manifestation[19]. However, it is important to emphasize that only four individuals composed the acyclovir group of treatment in the present study, which highlights the necessity of further investigations for a more definitive conclusion.

Although the authors strongly believe that the evidence provided this clinical study could help healthcare professionals and authorities to developed medical conducts to manage HSV oral and perioral infections, this study presented some limitations mainly regarding study design and sample size of G2 and G3. Methodological limitations related to study design are related to (1) sample collection, which was by convenience sample due to the necessity of HSV manifestation; and (2) group arrangements, which was performed in a non-randomized way due to differences in the profile of individuals required (immunocompetent *vs.* oncologic). Besides, the limited sample sized hampered a more definitive conclusion about the differences between the efficacy of APDT and acyclovir treatment. Therefore, the authors alert for the possible presence of bias related to these methodological aspects.

Within the limitations of this study, it is possible to conclude that APDT is an effective adjuvant treatment for HSV oral and perioral infections in both

immunocompetent and oncologic individuals. Oncologic individuals presented a slower response to the therapy than immunocompetent ones. Also, APDT seems to be more effective for HSV lesions than topical acyclovir treatment, however further studies are necessary for a more definitive conclusion about this topic.

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