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High-Intensity Laser and Photodynamic Therapy as a Treatment for Recurrent Herpes Labialis

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Abstract

Objective: The aim of this study was to report the treatment of recurrent herpes labialis (RHL) using a high-intensity laser or methylene blue (MB)-mediated photodynamic therapy (PDT) in combination with low-level laser therapy (LLLT). ***Materials and Methods:*** Four clinical cases of patients diagnosed with RHL are described in this report. Two patients were subjected to high-intensity laser therapy (HILT) followed by LLLT, and two patients received MB-mediated PDT, again followed by LLLT. LLLT was conducted at 24, 48, 72 h, and 7 d after HILT or PDT. Patients were followed up after 6 mo. ***Results:*** Throughout the follow-up period, all patients reported pain relief and did not show any signs or symptoms of RHL. A favorable healing process was observed in all cases. None of the patients reported pain as a consequence of the treatment. ***Conclusion:*** These results suggest that HILT and MB-mediated PDT, in combination with LLLT, may constitute a benefit when treating vesicles in RHL.

Introduction

Recurrent herpes labialis (RHL) is one of the recurrent herpes simplex virus (HSV-1) infections and occurs in 20–40% of the population.[1,2] It has a well-known clinical course that begins with prodromal signs or symptoms, such as burning or swelling, which are usually noticed by the patient. The vesicles can develop in the corresponding area and progress to ulceration and crusting within 72–96 h.[3] The most common treatment for RHL is based on antiviral compounds, such as acyclovir or valacyclovir. However, the intermittent administration of acyclovir can promote drug resistance. It also only yields a good response if applied before the onset of the vesicles.[4–6] Previous work has shown that photodynamic therapy (PDT) can be effective in the inactivation of HSV in vivo.[7]

The present study describes the results of four clinical cases in which PDT or high-intensity laser therapy (HILT) was used in combination with low-level laser therapy (LLLT) to treat RHL.

Case Reports

Patients were referred to the Special Laboratory of Lasers in Dentistry (LELO) of the School of Dentistry at the University of São Paulo, Brazil, presenting with lesions on the upper or lower lips, previously diagnosed as RHL. All patients signed an informed consent concerning the treatment of RHL using lasers. Table 1 shows the clinical information about the described cases, concerning the duration of the complaint and the recurrence of RHL before and after the laser treatment in a 6-mo follow-up period.

Case 1

A 22-year-old female presented with vesicles on the upper lip (Fig. 1A). The patient was treated with the Er,Cr:YSGG laser (Waterlase Millennium, Biolase Technology, Inc., San Clemente, CA) for drainage of the vesicles. The equipment has a wavelength of 2.78 μm, a pulse duration of 140–200 μs, and a fixed repetition rate of 20 Hz (Fig. 1B). The power output of the laser was set at 0.75 W, and was previously checked with

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Table 1. Description of Clinical Information

Case	*Duration of complaint (years)*	*Frequency of recurrence before laser treatment*	*Frequency of recurrence after laser treatment**
1	7	3 times per year	No
2	4	4 times per year	No
3	10	Once a month	No
4	6	5 times per year	No

*At the 6-month follow-up, no recurrence was observed for any patients.

a Power Meter (Power Max 600, Molectron, Coherent; Santa Clara, CA). The delivery system consisted of a fiber-optic tube terminating in a handpiece with a sapphire tip 600 μm in diameter. An air-and-water spray was set at 10% and 15%, respectively. The spot size at the tip was 0.0028 cm^2. Twenty-four hours after HILT, LLLT was conducted using a diode laser with a continuous emission of a 660-nm wavelength red light and a spot size of 0.04 cm^2 (Twin Flex II, MM Optics, São Carlos, SP, Brazil). The energy density was 3.8 J/cm^2 per point, with a power output of 15 mW, and 0.15 J of energy per point, delivered in three points through the punctual technique, in contact. The power output was previously checked with a Power Meter (841-PE, Newport Corp., Irvine, CA). LLLT was conducted at 24, 48, and 72 h, and 7 days after HILT. After vesicle drainage, pain relief was achieved. After 48 h, a crusting area was noticed (Fig. 1C). After 1 week, an advanced healing process could be observed (Fig. 1D). After 2 weeks, there were no signs or symptoms that could be related to RHL (Fig. 1E). The patient was observed monthly, and there was no recurrence in a 6-month follow-up period.

Case 2

An 18-year-old male showing vesicles on the upper lip (Fig. 2A) was treated with HILT for drainage of the vesicles, and the irradiation protocol was the same as described in case 1 (Fig. 2B and C). Following HILT, LLLT was conducted with the same parameters as for case 1 (Fig. 2D) except that four points of irradiation were considered, due to a greater

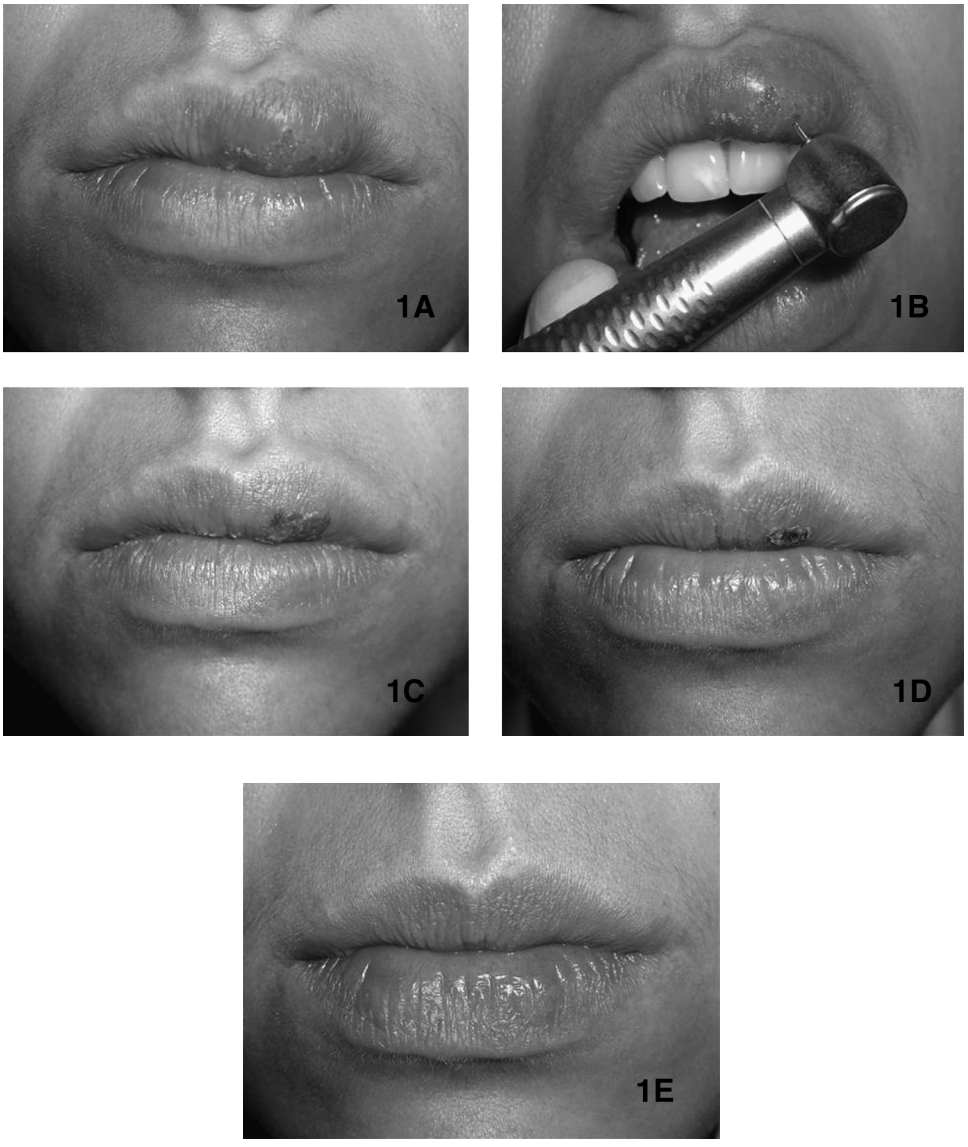

FIG. 1. Initial aspect of vesicles on the upper lip (**A**). Irradiation with an Er,Cr:YSGG laser (**B**). Lesion aspect after 48 h (**C**), 1 week (**D**), and 2 weeks (**E**).

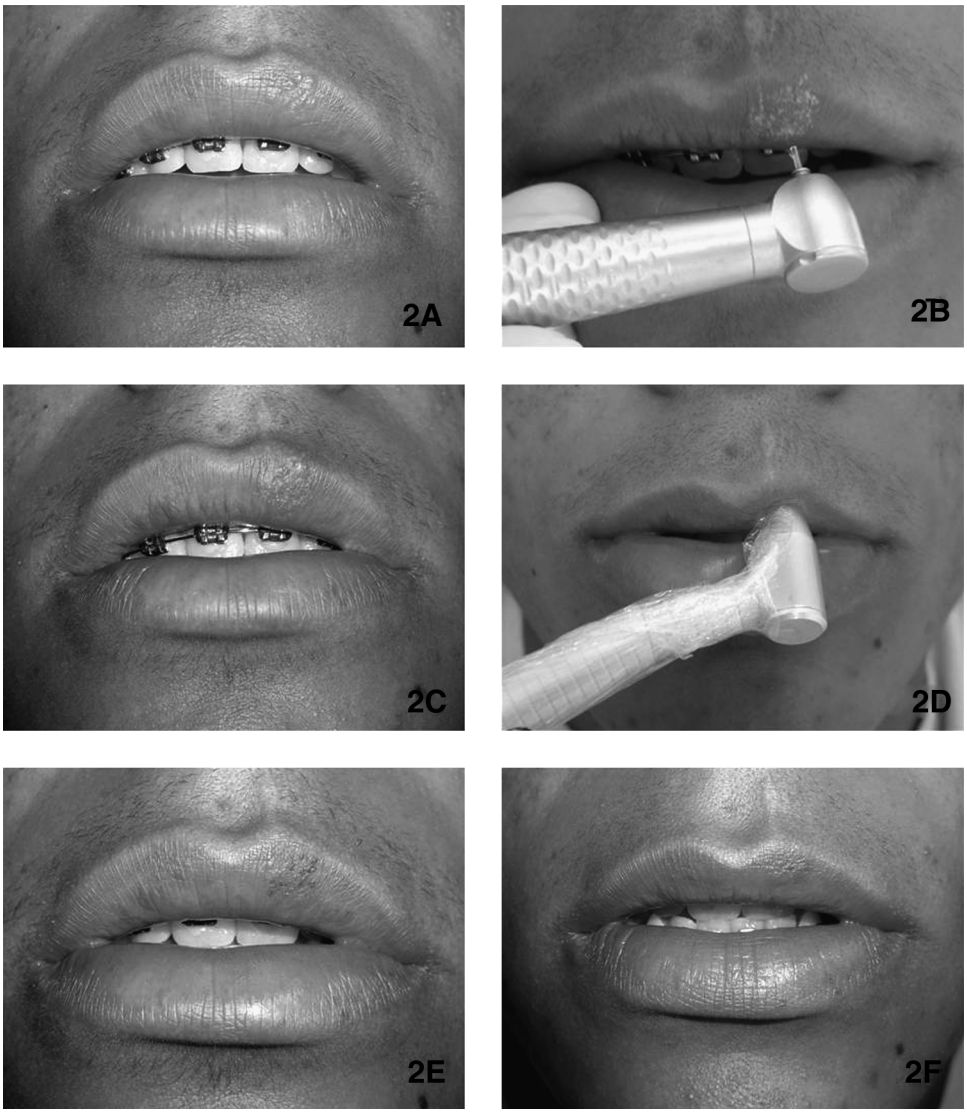

FIG. 2. Initial aspect of RHL on the upper lip (**A**). Drainage of vesicles with an Er,Cr:YSGG laser (**B**). Aspect of vesicles after drainage (**C**). LLLT irradiation after 24 h (**D**). Presence of a crusting area after 48 h (**E**). One week after HILT irradiation (**2F**).

lesion area. A crusting site was noticed 48 h after HILT (Fig. 2E). After 1 week, the patient showed no signs or symptoms related to RHL (Fig. 2F). During the 6-month follow-up, no recurrence was observed.

Case 3

A 23-year-old woman, presenting with vesicles on both upper and lower lips, reported local pain, discomfort, and also an itching sensation that began 1 d before the scheduled appointment (Fig. 3A). The vesicles were perforated using a sterilized needle. Drainage was performed through slight and intermittent movements with sterilized gauze until the fluid stopped draining. Note that this procedure should be performed with caution to avoid spreading the infection to the adjacent area. So, in this case, it was extremely important to watch the fluid and keep the sterilized gauze around the area of the lesion. Methylene blue (MB) dye solution at a concentration of 0.01% (m/V) was applied into the already dried vesicles, and LLLT was performed 5 min after the dye application (Fig. 3B). PDT was performed using a diode laser with a continuous emission of a 660-nm wavelength red light (Photon Lase III, DMC, São Carlos, SP, Brazil). The energy density was 100 J/cm^2, the power output was 100 mW for 28 s per point, and 2.8 J of energy with a spot size of 0.028 cm^2 delivered through the punctual technique, in contact (Fig. 3C and D). The total energy delivered was 8.4 J, equally divided between the three points for each vesicle. Sessions of LLLT were performed at 24, 48, and 72 h, and 7 d after PDT. After 24 h, crusts could already be noticed (Fig. 3E). The LLLT consisted of irradiating the same area with a total delivered dose of 20 J/cm^2, a power output of 40 mW for 14 s per point, and 0.56 J of energy per point. The device used was the same as that described for the PDT technique. Seven days after the PDT session, the patient showed no clinical signs of the previous HSV lesion (Fig. 3F). After concluding the treatment, the patient returned once a month, for a period of 6 months, without reporting any recurrence of the lesion.

Case 4

A 21-year-old male, showing vesicles on the lower lip, mentioned pain and discomfort as a consequence of the RHL

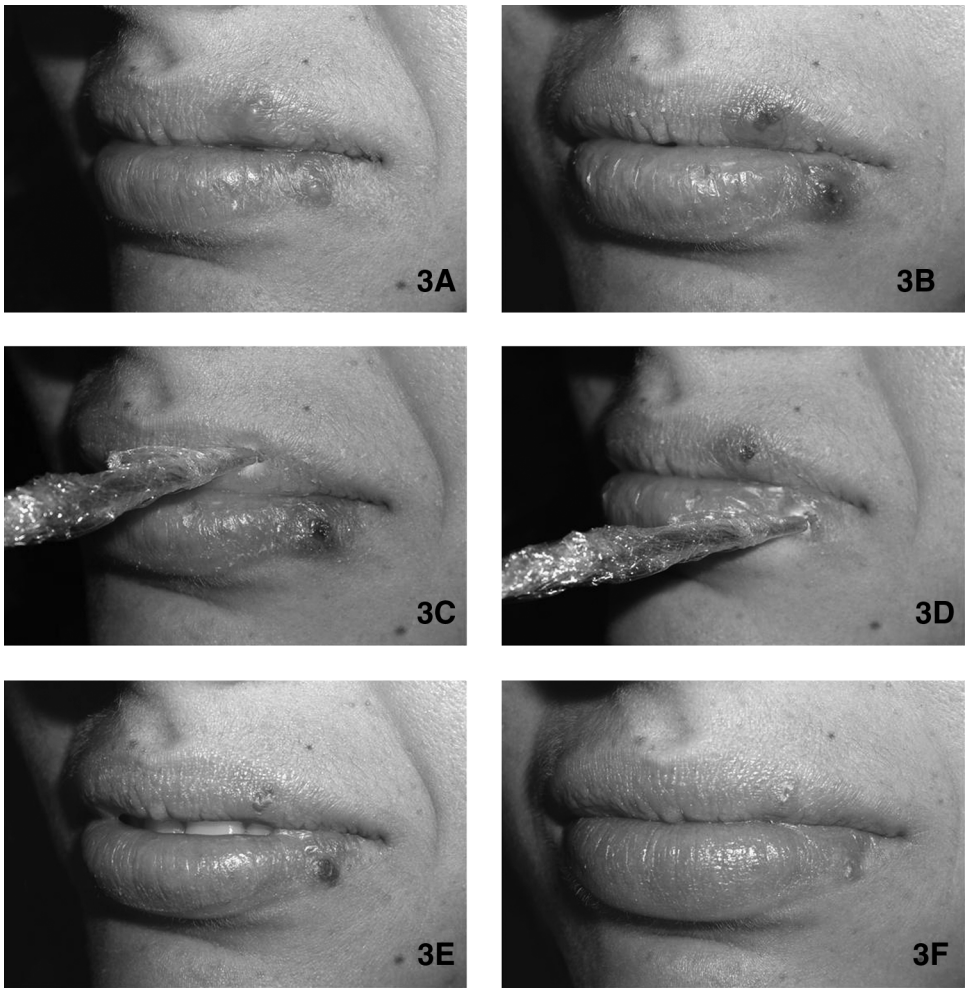

FIG. 3. Initial aspect of RHL on the upper and lower lips (**A**). Application of MB 0.01% (**B**). After 5 min, PDT performance on three points of each lesion (**C** and **D**). Aspect of the lesion after 48 h (**E**). One week after, the lesions had healed (**F**).

episodes due to long periods of exposure to sunlight (Fig. 4A). The PDT parameters were the same as that described in case 3, due to the greater lesion size. Irradiation was performed at five points. Thus, the total delivered energy was of 14 J, equally divided between the five points. After drainage of the vesicles (Fig. 4B), the MB dye solution was applied for 5 min (Fig. 4C). The LLLT followed the same protocol as described in case 3, but five points were irradiated, totaling 2.8 J (Fig. 4D). After 48 h, a crusting site was noticed (Fig. 4E), and after 7 d, the patient presented no clinical signs or symptoms (Fig. 4F). He was followed up monthly and did not show any signs of recurrence in 6 months.

Discussion

Antiviral drugs, such as acyclovir and valacyclovir, are the most common and accepted treatment for RHL. The discovery and development of acyclovir in 1982 resulted in a major advancement in the treatment of HSV and varicella zoster virus (VZV) in mild infections, as well as in severe infections of immunocompromised patients. Acyclovir is the prototype of a group of antiherpetic medications that needs to be phosphorylated intracellularly by a viral kinase in order to become effective inhibitors of viral DNA synthesis.[8] Arduino and Porter (2006)[9] reviewed the literature to evaluate the advantages and limitations of the therapy for HSV-1 infection. The authors reported that topical application of acyclovir (ACV) at 5% seems to be the accepted standard therapy for herpes labialis, being both effective and tolerated, although topical application of pencyclovir 1% has been proposed as a potentially useful treatment. Systemic ACV may be effective in reducing the duration of symptoms of recurrent HSV-1 infection, but the optimal timing and dose of the treatment are still uncertain. However, resistance to acyclovir may develop following alteration in either viral thymidine kinase or the DNA polymerase. Occasionally, headache, gastralgia, and nausea have been reported as side effects. Another disadvantage is that they cannot be used and are not suitable for all stages of herpes labialis.[10–12]

HILT can be used to promote rupture and to drain vesicles. Furthermore, it is hypothesized that HILT can reduce the amount of virus present in the fluid by increasing the local temperature and, consequently, decreasing the frequency and duration of the infection. However, to conclude this hypothesis, it is necessary to perform more studies concerning the inactivation of the virus, and also perform clinical trials to observe the frequency and recurrence of the lesions.

The Er,Cr:YSGG laser equipment used in these clinical cases has an air-water spray that is able to reduce pain during irradiation. Lasers without a cooling system, such as

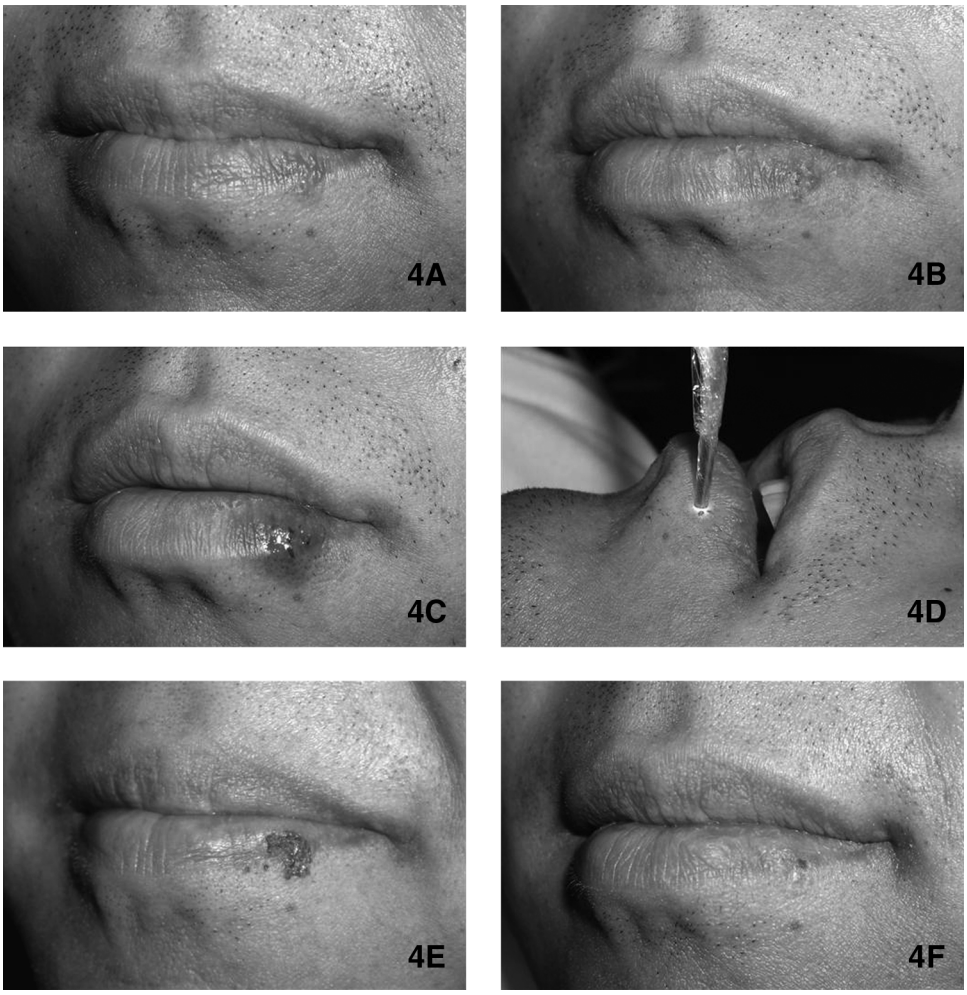

FIG. 4. Initial aspect of RHL on the lower lip (**A**) and after drainage of the vesicles (**B**). MB dye solution application (**4C**), irradiation 5 min after MB dye solution application (**D**). Aspect of the already formed crust after 48 h (**E**). One week after PDT treatment (**F**).

the Nd:YAG and diode lasers, may result in more discomfort for the patient during irradiation. On the other hand, PDT appears to be an effective therapeutic option, and it does not have the heating issue inherent to high-intensity laser techniques. Moreover, PDT is a less expensive technique when compared to HILT.[9,13]

Like other viruses, the herpes viruses undergo photodynamic inactivation.[13–16] The photodynamic interaction demands a photosensitizer (PS) and a light source that interacts with the chosen PS. The treatment of clinical cases 3 and 4 involved the use of MB, a phenothiazine dye that has been used for several years in medical practice and is recognized as having viral photoinactivation properties.[17–20] In low concentrations, MB has no tissue toxicity and can be given topically or intravenously without toxic side effects.[17–21] This dye has been used for the PDT of tumors and precancerous lesions in the oral mucous membrane.[22,23] Additionally, a recent study concluded that MB-mediated PDT treatment of oral candidiasis is a potential treatment alternative to traditional antifungal drug therapy. The authors also reported that MB-mediated PDT for the treatment of mucocutaneous oropharyngeal candidiasis would be a non-toxic, simple, inexpensive, and repeatable therapy without the risk of fungal resistance.[24]

The PDT mediated by MB may show some important advantages over the antiviral compound-based treatment for RHL. Acyclovir showed a significant response for treatment of RHL only when applied before the onset of the vesicles.[6] Two studies agree that perhaps the current dosage forms of acyclovir do not produce a sufficient tissue level.[6,25] This may be because acyclovir is not well absorbed by either the oral or topical routes.[26,27] In addition, the intermittent administration of acyclovir does not alter the frequency of recurrences,[28] while LLLT may reduce their incidence.[29,30]

Thus, MB-mediated PDT used in combination with LLLT may be an eligible treatment for RHL, once it is a non-invasive treatment modality and less expensive than ALA-PDT, and it could also act in the vesicle stage, giving relief to patients, as previously reported.

Conclusion

The present clinical case reports have shown the efficacy of HILT or MB-mediated PDT, in combination with LLLT, on the treatment of herpes labialis. All patients considered the technique painless and comfortable. The healing process was favorable, and there was no recurrence of the lesions during the 6-mo follow-up. Further studies, including double-blind

randomized clinical trials, with a greater number of patients are necessary to reach an established protocol.

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Author Disclosure Statement

No competing financial interests exist.

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