

## Case Report

# Photodynamic Therapy Can Be Effective as a Treatment for Herpes Simplex Labialis

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### Abstract

**Background Data and Objective:** Herpes is a common infectious disease that is caused by human herpesviruses. Several treatments have been proposed, but none of them prevent reactivation of the virus. This article describes the use of photodynamic therapy (PDT) as a treatment for herpes lesions, and reports on four cases.

**Materials and Methods:** PDT was used as an adjuvant therapy for the treatment of herpes labialis in four patients. A special type of 0.01% (m/V) of methylene blue solution was applied to the vesicular stage of herpesviral disease and the lesions were irradiated with laser energy (wavelength 660 nm, energy density 120 J/cm<sup>2</sup>, output power of 40 mW, 2 min per point, 4.8 J of energy/point, at four points). After 24 h the patients returned and phototherapy was repeated with the same equipment, this time with 3.8 J/cm<sup>2</sup> and 15 mW, for a total dose of 0.6 J. The same procedure was repeated 72 h and 1 wk later.

**Results:** Treatment with low-level laser therapy can be considered as an option in the treatment of herpes labialis, and decreases the frequency of vesicle recurrence and provides comfort for patients. No significant acute side effects were noted and the lesions healed rapidly.

**Conclusion:** Treatment of herpes labialis with PDT was effective, had no side effects, and when associated with laser phototherapy, accelerated the healing process.

### Introduction

**H**ERPES SIMPLEX VIRUS-1 (HSV-1) is a DNA virus that causes primary herpetic gingivostomatitis, mucocutaneous orofacial disease, and ocular disease. Recurrent lesions are common on the face and lips, and less common, intraorally.<sup>1</sup> Occasional cases are caused by HSV-2, and HSV-1 may also present as a primary genital infection.<sup>2</sup> The infection usually occurs in children, adolescents, and young adults.<sup>3</sup> Transmission is via direct contact with infected secretions and the majority of primary infections are subclinical.<sup>1</sup>

Recurrent herpes labialis occurs in 20–40% of the population,<sup>4</sup> and the lesions are commonly referred to as “cold sores” or “fever blisters.” Patients notice a prodrome of tingling, itching, or burning, followed by a papule that progresses to vesicular, crusted, and healing stages; the outer one-third of the lips are the most frequently affected areas.<sup>5</sup> Although a number of treatments have been studied, anti-

viral chemotherapy has not been effective in the treatment of herpes labialis.<sup>6</sup> Acyclovir (ACV) and penciclovir are the most commonly used medications to prevent or suppress recurrent HSV-1 flares. An over-the-counter formulation (e.g., acyclovir for topical application) is used by most patients.<sup>5,7,8</sup> However, the continuous use of these medications raises the possibility of development of a drug-resistant viral strain.<sup>3,5</sup> Other therapeutic approaches that have been used in attempts to cure HSV-1 infections include cryotherapy and use of vitamins in order to increase immune system resistance.<sup>9,10</sup>

High-power lasers (HPL) have been used for the treatment of herpes labialis in its vesicular stage, while low-power lasers (LPL) are used to accelerate the healing process and minimize the frequency of vesicle formation. However, many patients report pain during HPL treatment due to the increase in temperature. Moreover, in comparison with LPL, HPL is more expensive.<sup>11</sup>

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Photodynamic therapy (PDT) is based on the interaction of a photosensitizer and light in oxygenated tissue.<sup>12,13</sup> Damaging or killing a biological system by photo-oxidation is known as "photodynamic inactivation," "photodynamic effect," or "photodynamic therapy." Several studies report virus inactivation by means of PDT.<sup>6,9,14</sup> The antiviral effect is dependent on the dye concentration, the light source, and the substrate. Methylene blue (MB) is one of the photosensitizers that can be used for the treatment of herpes labialis by PDT with satisfactory results.<sup>6</sup>

The great advantage of PDT for the treatment of herpes labialis is that the technique is specific, painless, and affordable. Furthermore, low-level laser therapy accelerates the healing process and decreases the frequency of lesions.<sup>15-20</sup>

Therefore, this article presents clinical reports of cases in which PDT was used for the treatment of herpes labialis.

## Materials and Methods

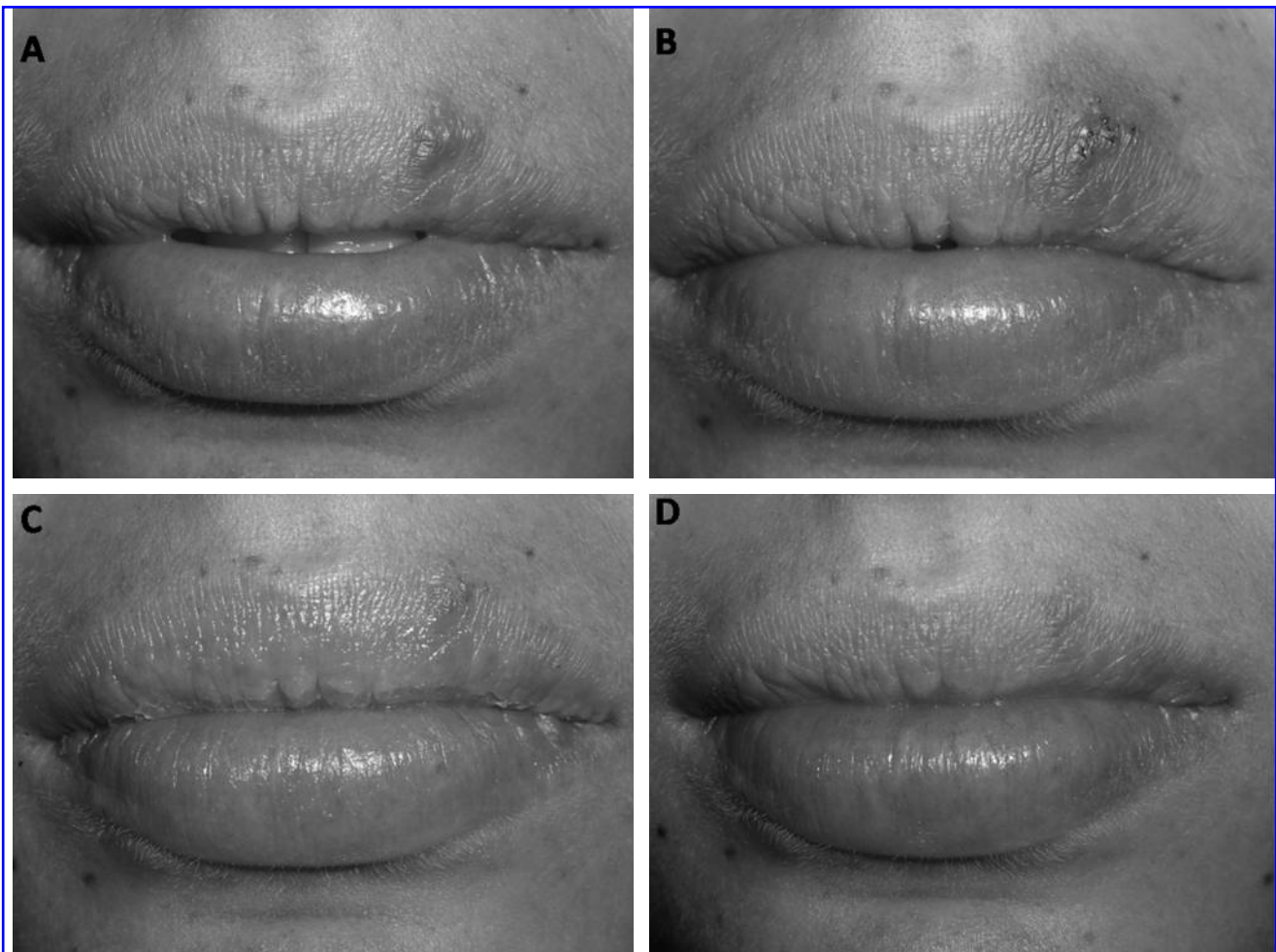
### *Photodynamic therapy*

Four patients referred from LELO (Special Laboratory of Lasers in Dentistry at the School of Dentistry of the University of São Paulo) signed an informed consent for the treatment of herpes labialis. All patients were in the vesicular

stage, so it was possible to perform PDT treatment on the lesions. The vesicles were carefully perforated with a sterilized needle so that the liquid could flow. A small cotton ball soaked in a 0.01% (m/V) methylene blue solution was placed over the lesion, and after 5 min, the excess dye was removed. The lesions were irradiated with a 660-nm LPL (Twin Laser; MM Optics®, São Carlos, Brazil) with a spot size of 0.04 cm<sup>2</sup>, in continuous mode. Energy density was 120 J/cm<sup>2</sup>, power output was 40 mW, for 2 min per point for 4.8 J of energy, in contact mode. The total delivered energy was 19.2 J, equally divided among four different points. After 24 h the patients returned and the phototherapy was performed with the same LPL, at an energy density of 3.8 J/cm<sup>2</sup>, 15 mW power output, for a total of 0.6 J of energy, divided over the same four points. The phototherapy regimen was repeated after 72 h and 1 wk. No pain or discomfort was reported during treatment. Patients returned for follow-up appointments during the following 6 mo after treatment. The clinical cases are shown in Figs. 1, 2, 3, and 4.

### *Case reports*

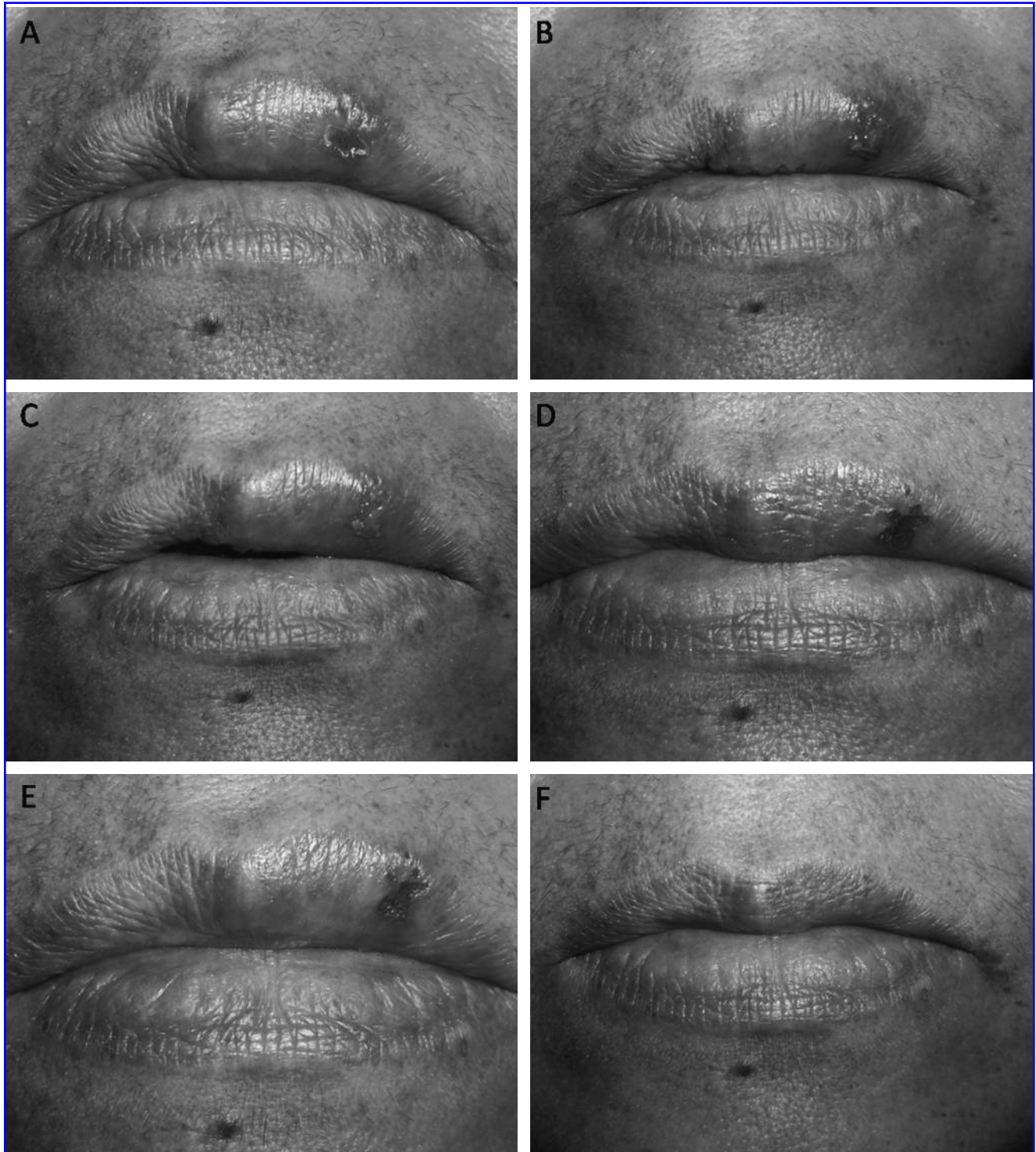
**Case 1.** The patient, a 22-year-old Caucasian woman, presented with vesicular herpes labialis on the upper lip. This



**FIG. 1.** (A) Herpes lesion before PDT. (B) Same lesion after dye application. (C) Same lesion 24 h post-treatment. (D) Same lesion 1 wk post-treatment.

patient complained of having monthly vesicle outbreaks. Fig. 1A shows the lesion before PDT. After dye application (Fig. 1B) and PDT, it was observed that after 24 h the lesion was almost healed (Fig. 1C). After 1 wk (Fig. 1D) the lesion was completely healed. This patient had a recurrence 4 mo post-treatment.

**Case 2.** The patient, a 52-year-old Caucasian woman, had vesicular herpes on the upper lip, and the lesion had a crust due to the topical application of acyclovir. Fig. 2A shows the initial appearance of the lesion. Fig. 2B shows the perforated vesicle and dye application. Fig. 2C shows the lesion post-irradiation. The photo in Fig. 2D was taken 6 h post-irradiation.



**FIG. 2.** (A) Initial vesicle. (B) Perforated vesicle and dye application. (C) Same vesicle immediately post-irradiation. (D) Same vesicle 6 h post-irradiation. (E) Same vesicle 24 h post-irradiation. (F) Same vesicle 1 wk post-treatment.



ation. It can be seen here that the crust had already formed. Fig. 2E shows the lesion after 24 h, with satisfactory healing. Complete healing of the lesion was seen after 1 wk (Fig. 2F). This patient had no recurrences at 10-mo follow-up.

**Case 3.** The patient, a 21-year-old Asian man, had vesicular herpes of the left lower lip. In Fig. 3 we can see the healing process. After 1 wk it was almost completely healed, but some redness remained because the crust was accidentally removed. This patient had no recurrences at 6-mo follow-up.

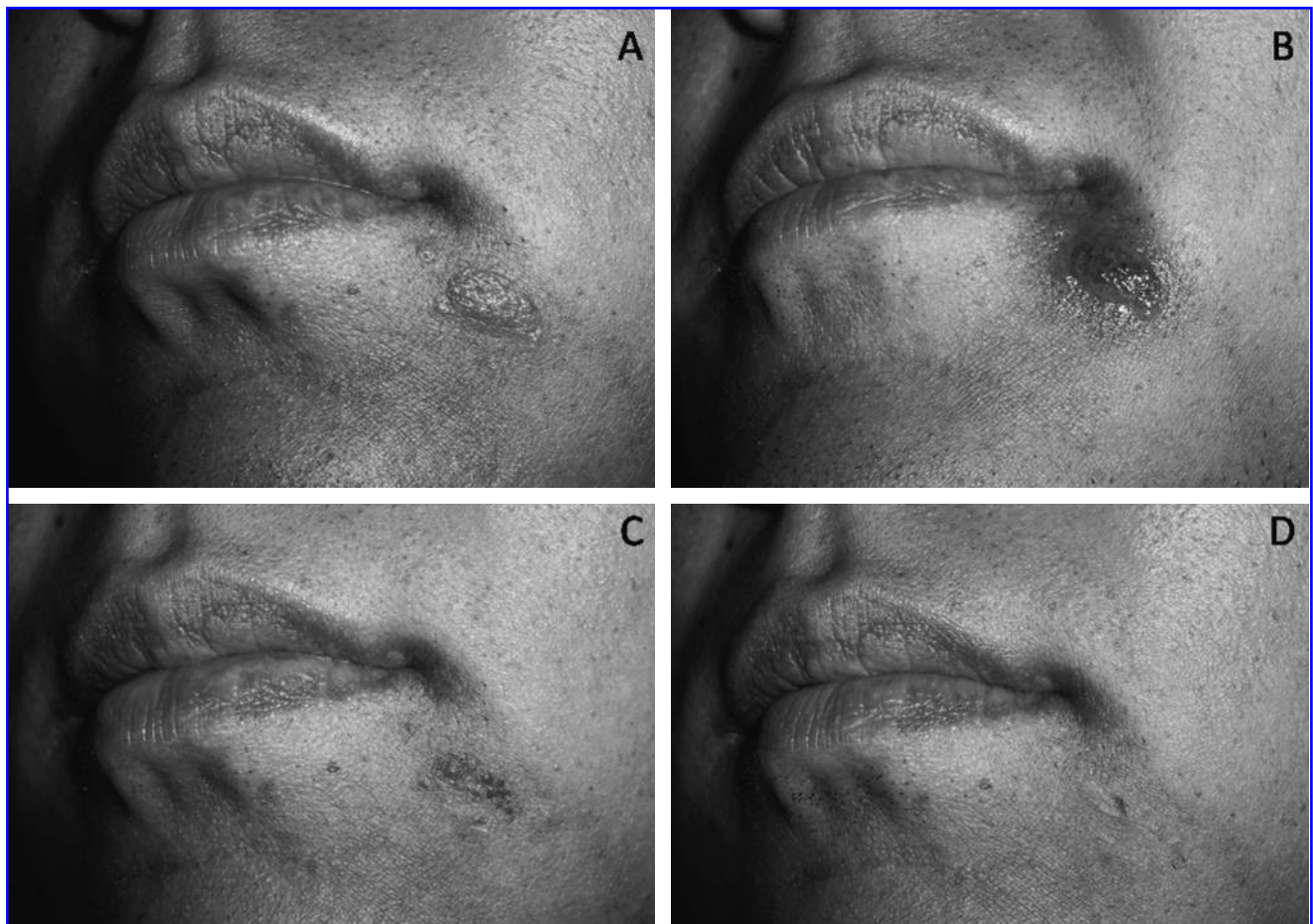
**Case 4.** The patient, a 25-year-old Caucasian woman, had vesicular herpes on her upper lip. Fig. 4 shows the steps used for treatment; the lesion was completely healed after 1 wk. This patient had no pain or discomfort during the treatment process, and she had no recurrence at 6-mo follow-up.

### Discussion

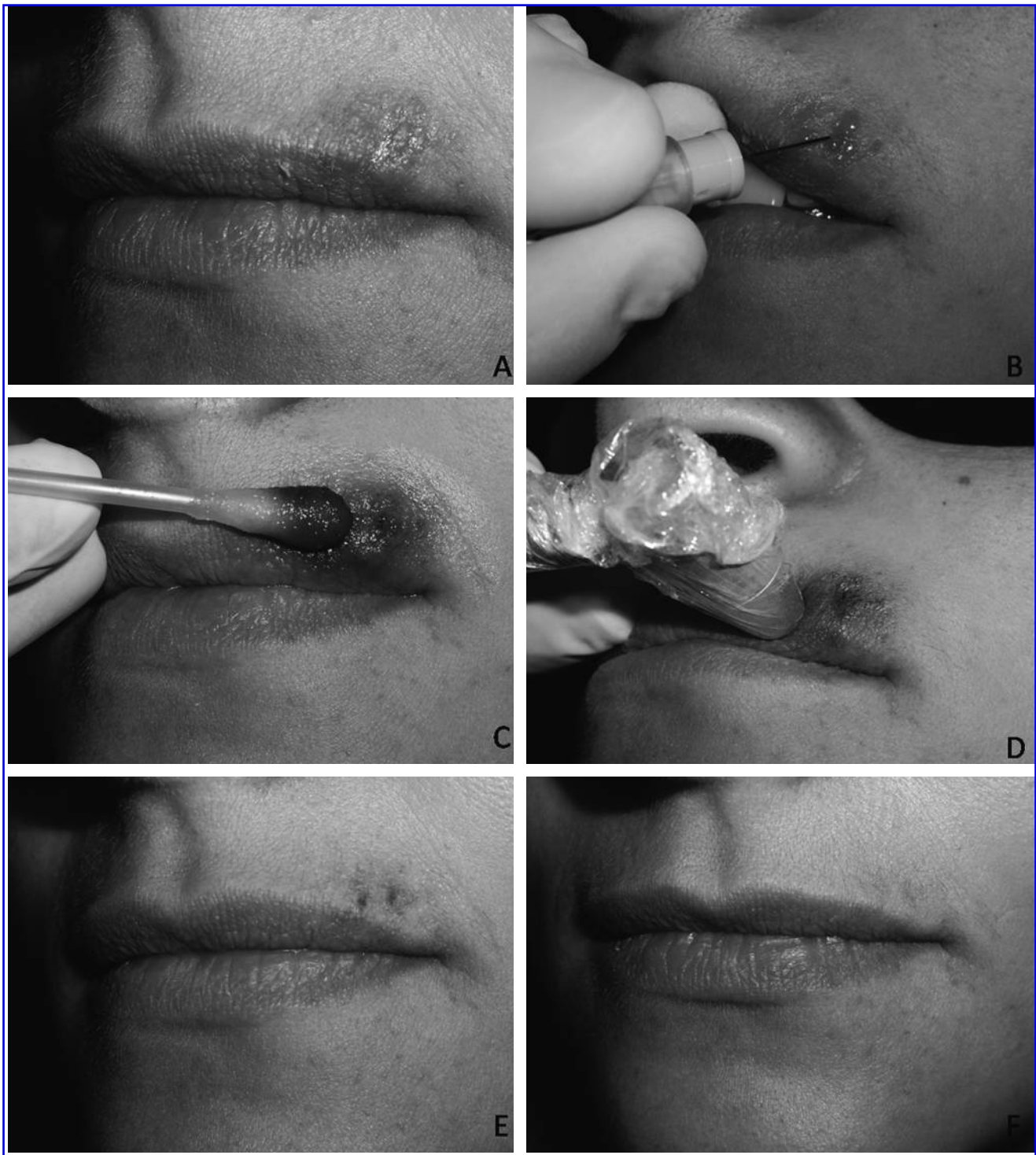
The conventional procedure for the treatment for herpes labialis is to prescribe medication. However, the medicine can cause resistance and side effects, and it cannot be used for all stages of herpes labialis. Arduino and Porter<sup>18</sup> ana-

lyzed the published literature to evaluate the advantages and limitations of therapy for HSV-1 infection. These authors reported that topical application of ACV at 5% appears to be the accepted standard therapy for herpes labialis, being both effective and well-tolerated, although topical application of penciclovir 1% has also 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 dosing remain unclear. Acyclovir and famciclovir may be of benefit in the acute treatment of severe HSV-1 disease in immunocompromised patients. There is also evidence that prophylactic oral ACV may reduce the frequency and severity of herpetic flares in immunocompromised patients.<sup>3,18</sup>

Another treatment option for HSV-1 is phototherapy.<sup>11</sup> High- and low-power lasers either associated with PDT or not can be used. The choice of therapy should be made according to the stage of the lesion. When the lesion is at the vesicular stage, HPL or PDT must be used. When crusts have already formed, LPL at the red wavelength can be used, with the aim of accelerating the healing process. An infrared laser can also be used at the crusting stage when edema is present, or when there is no infectious process. Various proto-



**FIG. 3.** (A) Initial lesion. (B) Application of methylene blue dye solution before irradiation. (C) Same lesion 24 h post-treatment. (D) Same lesion 1 wk post-treatment. Redness is seen here because the crust was accidentally removed.



**FIG. 4.** (A) Initial lesion. (B) Perforation of the lesion. (C) Application of the dye solution. (D) Irradiation with the low-power laser. (E) Same lesion 24 h post-treatment. (F) The lesion was completely healed after 1 wk.

cols for irradiation are discussed in the literature; however, there is no consensus among authors.<sup>11,19</sup>

High-power lasers can be used to rupture and drain vesicles. Furthermore, it is hypothesized that irradiation can reduce the quantity of virus present in the fluid, decreasing the frequency and duration of infections. The use of a water spray can reduce pain during irradiation, but some lasers,

such as the Nd:YAG and diode lasers, do not have a cooling system.

On the other hand, PDT appears to be an effective therapeutic option. Although the photodynamic effect was demonstrated against viral targets more than 70 y ago, the use of photosensitizers as antivirals *in vivo* has been slow to gain acceptance. The reason may be due to the pronounced side



effects seen in several cases of the phototreatment of herpes genitalis in the early 1970s.<sup>14</sup> With the development of photodynamic therapy to treat cancer or localized infections, a great deal of experience has been gained in the targeting and eradication of viruses. Photosensitized oxidation is a reaction in which a sensitizer that has been excited by light causes a substrate to be oxidized by molecular oxygen. The substrate may be a simple organic molecule (an unsaturated or aromatic compound), or it may be a macromolecule (DNA, RNA, protein, lipid, or carbohydrate), isolated from or part of a living system. The sensitizer may be endogenous or exogenous to the system. The excitation wavelengths are dependent upon the absorption spectrum of the sensitizer and should be in the visible range. In general, the active spectrum for the photodynamic oxidation of a substrate mimics the absorption spectrum of the particular sensitizer being used rather than that of the substrate. Oxygen concentrations as low as 10  $\mu$ M are sufficient for photo-oxidation to occur. The rate of sensitized photo-oxidation of simple organic molecules is dependent on (1) light parameters, (2) substrate concentration, (3) sensitizer concentration, (4) oxygen concentration, and (5) pH.<sup>9,12</sup>

Successful PDT always involves the optimization of a large number of parameters. Obviously, selection of an effective photosensitizer with resonant absorption by the light source being used is essential for the success of the technique. The most common light sources used are lasers, specially red and near-infrared lasers, because of their advantages. Lasers produce monochromatic light of a single wavelength, and the proper light dosimetry is easy to calculate and the laser beam can be passed through an optical fiber for localized treatment.<sup>21</sup>

Among the substances employed in photodynamic procedures to inactivate HSV are found proflavines,<sup>22</sup> porphyrins such as hematoporphyrin derivatives,<sup>23</sup> and aminolevulinic acid (5-ALA). When 5-ALA is exogenously supplied, protoporphyrin IX accumulates in various cells and makes them light-sensitive.<sup>24</sup>

The virucidal properties of photoactive phenothiazine dyes such as methylene blue have been known for 70 y. The mechanism of virus inactivation involves binding of the dye to nucleic acid, absorption of light, generation of reactive oxygen species, and guanine oxidation in the viral genome.<sup>25</sup> Some studies have clearly demonstrated the effect of MB against viruses.<sup>6,26</sup> Also, MB shows strong absorption at the red end of the visible spectrum.

Defining protocols for the clinical application of PDT is not an easy task, since this therapeutic modality is affected by several light dosimetric parameters, such as wavelength, power output, exposure time, fluence rate, fluence (dose), number of treatments, and treatment intervals. In addition to the light source parameters, the photosensitizer chemical and photophysical properties should be considered, as well as the dye concentration and dye solvent used.

In this study, the four clinical reports demonstrated the efficacy of PDT in the treatment of herpes labialis. All patients found the technique to be painless and comfortable. Healing was accelerated and the recurrence of lesions decreased significantly.

As PDT is not yet being widely used by dentists or physicians, further studies are necessary and follow-up clinical reports are required. Despite all the indications, only a small

number of clinical studies are reported in the literature with regard to PDT treatment for HSV. PDT has proven to be an effective alternative to chemical agents against microbial infections. It is a local treatment that may be a useful alternative for the treatment of herpes labialis.

## Conclusion

With the parameters used here, treatment of herpes labialis by means of photodynamic therapy was effective, had no side effects, and when associated with laser phototherapy, accelerated the healing process of herpetic lesions.

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