



RESEARCH ARTICLE

TREATMENT OF ORAL HERPES SIMPLEX VIRUS INFECTIONS BY PHOTODYNAMIC THERAPY WITH A DIODE LAMP: A PILOT STUDY

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ABSTRACT

**Introduction:** Or HSV) infection is one of the most common oral solution. Many topical and systemic therapies are reported to be effective in lesions treatment. Scientific Literature reported many cases of recurrent herpes lesions successfully treated with photodynamic therapy (PDT). PDT is based on the interaction of a photosensitizer and light irradiation in oxygenated tissue. This combination leads to arelated bacterial cell damage. Methylene blue (MB) and Toluidine blue are the most used photosensitizers. We want to propose a pilot study with 10 patients for the treatment of Herpes simplex infection with photodynamic therapy effected by a 630nm diode lamp and associated photosensitizer.

**Materials and Methods:** Ten patients are included in this pilot study, 4 of them with herpes simplex lesions on the hard palate, 5 of the them in the lips, 1 in gingival tissues. All patients are treated with single sessions of photodynamic therapy performed by 630 nm length light irradiation and a Toluidine blue solution as a photosensitizer. A Toluidine-based fluid topical preparation was applied over each lesion and was exposed to 10 cycles of 30 seconds of LED light irradiation with long tip, remaining at about 0.5 cm from the lesion. Subsequently, a gauze is used to remove the dye. Results: All patients healed at day 7; 6 of them at day 2 are free of symptoms (3 in hard palate, 1 gum lesion, 2 in lips); 2 of them at the day 4 are completely healed (1 in hard palate, 1 in lip); 2 of them at the day 7 have no signs of lesions (in the lip).

**Conclusions:** In our study we found that the 630 nm diode lamp is safe and effective and reduce the time of healing of herpes simplex virus lesions.

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INTRODUCTION

Oral and perioral herpes simplex virus (HSV) infection is one of the most common oral soft tissue disease in the general population. HSV-1 serotype is the most common cause of orofacial infections. Primary oral HSV infections usually occur in early childhood and while the majority are subclinical, sometimes they are accompanied with general symptoms, such as fever and lymphadenopathy followed by vesicles and/or ulcers affecting a variety of intraoral surfaces, overall lips, hard palate and gum (Stoopler et al., 2013). Most primary oral HSV infections are readily diagnosed based on clinical history, signs and symptoms and further laboratory investigation is generally not warranted (Chi, 2015).

A lot of topical and systemic treatments are proposed for the prevention and the management of oral HSV. The most commonly recommended topical antiviral agents are Acyclovir 5 %, Penciclovir 1 % and Docosanol 10 % creams (Stoopler et al., 2013; Chi, 2015). A study shows that monocaprin with low-dose doxycycline offers an effective treatment for herpes labialis (Skulason et al., 2012) Lidocaine gel 2 %, viscous lidocaine 2 % or mixtures of topical anesthetic are proposed to reduce symptoms and pain, and some authors supports the use of sunscreen on the lips with at least 15 sun-protection factor (SPF) to decrease the risk of developing episodes of recurrent herpes labialis (Stoopler et al., 2013). In severe cases of primary oral HSV infection is important to prescribe systemic treatment, oral acyclovir 200 mg five times a day or 400 mg three times a day for 10 days, and also valacyclovir and famciclovir (Stoopler et al., 2013;

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Mubareka *et al.*, 2010). To avoid collateral events linked to the use of pharmacological therapy other devices are studied in the literature for the treatment of oral HSV like HLLT (high level laser therapy) and LLLT (low level laser therapy) (Marotti, 2010; Ferreira *et al.*, 2011). Photodynamic therapy is also proposed for the treatment of herpes labialis. Photodynamic therapy (PDT) is based on the interaction of a photosensitizer and a light in oxygenated tissue. Methylene blue (MB) and Toluidine blue are the most used photosensitizers. Damaging or killing a biological system by photo-oxidation is known as photodynamic inactivation. Several studies report virus inactivation by PDT. The antiviral effect is dependent on the dye concentration, the light source, and the substrate. The great advantage of PDT for the treatment of herpes labialis is that the technique is specific, painless, and affordable (Marotti *et al.*, 2009; Ramalho *et al.*, 2015). Low-level diode lasers were mostly used as the light emitting source to excite the photosensitizer, although, in principle, all type of lamps can be used if set on the specific excitement wavelength of the dye. Non-coherent light sources, as light-emitting diode lamps (LED), have some advantages in comparison to lasers: longer irradiation times are possible and lower costs and simpler to use (Mongardini *et al.*, 2014). We want to propose a pilot study with 10 patients for the treatment of Herpes simplex infection with a particular photodynamic therapy effected by a 630nm diode lamp. The use of this device has already documented in the literature especially in periodontal (Mongardini, 2014) and endodontic treatment (Asnaashari *et al.*, 2016), and is effective especially for its antibacterial effect.

## MATERIALS AND METHODS

Ten patients are included in this pilot study, 4 of them with herpes simplex lesions on the hard palate, 5 of the them in the lips, 1 in gingival tissues. All patients are treated with single sessions of photodynamic therapy performed by Fotosan 630 nm (Dentalica, CMS Dental, Denmark) and a Toluidine blue as a photosensitizer. Fotosan 630 nm is a device that emits a LED light used in combination with a photosensitive reagent (Toluidine blue in syringes with a concentration of 0.1 mg / ml). The basic principle of this therapy is represented by the photochemical reaction between a photosensitive substance and a light source that emits a specific light spectrum. Specifically, the photosensitizer binds to the surface of microorganisms and absorbs light of a specific wavelength taking energy. The received energy reacts with oxygen to form ROS (Reactive Oxygen Specimen) that is highly reactive and kills the microbial cell walls and internal structures. The principle LAD is effective not only against bacteria but also against microorganisms such as viruses, fungi and protozoa. The light-sensitive substances applied have very mild affinity with mammalian cells. For this there are no adverse effects during the treatments. The intensity of the light emitted diodes is between 2000 and 4000MW / cm<sup>2</sup>. There are 3 programs for its operation: with the green mode, we decide the seconds of application; the orange active mode cycles from 20 seconds, the red mode active cycles of 10 seconds. The fluid with Toluidine was applied over each lesion and was made 10 cycles of 30 seconds of LED light with long tip, remaining at about 0.5 cm from the lesion. Subsequently is removed the dye with gauze (fg1,2,3,4). The pictures of all the lesion's patients have been taken before the treatment, and after 1,2, 4 and 7 days. We evaluated the time of healing of each lesion and we calculated the average time of healing.



Fig. 1. Patient with oral herpes simplex infection on the palate



Fig. 2. Photosensitizer in the lesion

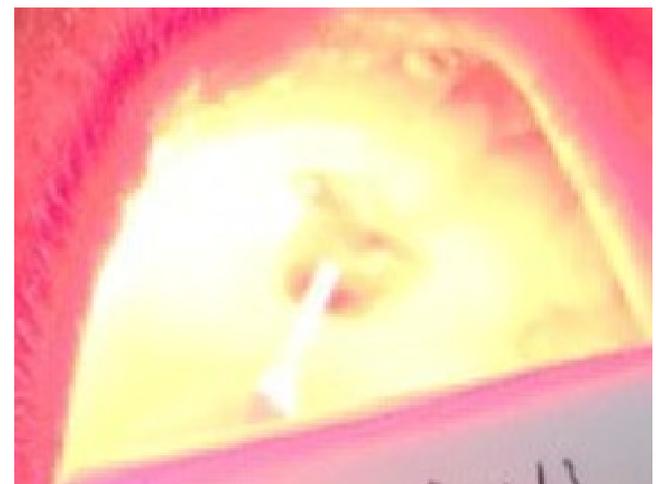


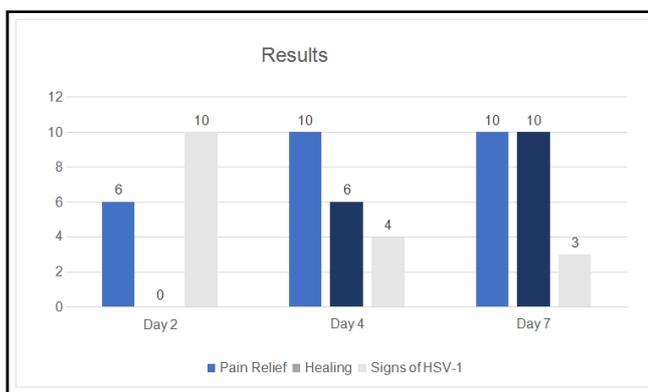
Fig. 3. LED light application

## RESULTS

All patients healed at day 7; 6 of them at day 2 are free of symptoms (3 in hard palate, 1 gum lesion, 2 in lips); 2 of them at the day 4 are completely healed (1 in hard palate, 1 in lip); 2 of them at the day 7 have no signs of lesions (in the lip). The average time of healing is 3,4 days, faster than values reported in literature (de Paula Eduardo, 2014; Pandeshwar, 2016) that



Fig. 4. Healing of the lesion after 4 days



are of 1 week. Faster healing times are found in palate and gum lesions. We found that phototherapy strongly decrease pain without causing any side-effects and the same conclusions are written in the recent literature (de Paula Eduardo, 2014).

## DISCUSSION

In a recent review of the Cocraine Library, the authors concluded that current evidence demonstrates that long-term use of oral antiviral agents like topical and systemic acyclovir, can prevent HSV, but the clinical benefit is small, and topical antiviral agents showed no efficacy or could not confirm their efficacy in preventing HSV (Chi, 2015).

In a study monocaprin with low-dose doxycycline (MCD) offers an effective treatment for herpes labialis, but there is no comparison with other topical and systemic drugs like acyclovir, penciclovir, valaciclovir. The authors concluded that although full enrolment to the trial was not achieved positive results for MCD, prodromal activity was statistically significant and MCD vesicle group showed also very good reduction in time to heal, but needed more subjects to support the results (Skulason *et al.*, 2012). Lidocaine gel 2 %, or mixtures of topical anesthetic are proposed to reduce symptoms but their use in pediatric population is controversial due to possible increased risk of life threatening events. Aspiration of topical lidocaine in this population has been linked to adverse neurologic and cardiovascular reactions, such as seizures and hypotensive episodes, respectively, while ingestion of topical benzocaine has been associated with development of methemoglobinemia (Stoopler, 2013).

Famciclovir is also proposed successfully but side effects like headache and nausea are connected with its use and data for its use in childhood and pregnancy are limited (Mubareka, 2010). Studies on HLLT and LLLT shows that these devices are effective for treatment of oral HSV but they are very few and overall case reports (Marotti, 2010; Ferreira, 2011; Muñoz Sanchez *et al.*, 2012). Works on photodynamic therapy for oral HSV therapy demonstrates that this type of treatment is effective and safe (Marotti *et al.*, 2009; Ramalho, 2015). PDT modulate metabolic processes by the conversion of the laser light energy into useful energy to the cell, in particular the light is absorbed by chromophores in the respiratory chain of the mitochondria, that increase reactive oxygen species (ROS), ATP synthesis and nitric oxide release. Moreover, there are immediate analgesic effects that could be due to physiological neural changes that strongly decrease pain (Pandeshwar, 2016). A recent work examined the use of PDT to treat herpesvirus infection (HVI) using an in vitro model. The authors concluded that had an antiviral effect on an in vitro model of HVI in cell culture. PDT has been shown to be effective treatment for HVI in vitro, leading to a reliable decrease of viral titer (Zverev, 2016). A review of the literature studies the effectiveness of Phototherapy on herpes virus cutaneous infections, including PDT. The conclusion is that light-based therapies can be considered a reasonable alternative in situations that preclude traditional drug-based therapies (Kelley, 2011).

Very few studies are conducted on Fotosan 630 device but its antimicrobial activity against *Enterococcus faecalis* is demonstrated in an in vitro study in which is more effective if compared to diode laser 810 nm irradiation (Asnaashari *et al.*, 2016). *E. faecalis* is resistant to calcium hydroxide and has the ability to adapt to varying conditions. PDT in this study significantly reduces the counts of *E. faecalis* in infected root canals compared to traditional endodontic instrumentation and irrigation treatment protocols. In a recent in vitro article a reduction of HSV-1 titer by 1000 times was determined (Makarov, 2014). We want to underline that herpetic lesions are found to be most susceptible to PDT during their prodromal stage and pain relief is immediate and the intermediate period between the attacks is prolonged (Pandeshwar, 2016). Advantages of photodynamic therapy include immediate effects, selectivity, access to complex areas, decreasing the possibility of bacteremia in immunocompromised systemic patients, decreasing patient discomfort, pain, and edema after surgery. Other 2 important points are time saving and avoidance of interfering with normal fora of adjacent tissues. Dentist is more exposed to contamination of oral HSV than the general population, and the idea of an effective local and safe treatment of herpes simplex that dentist could perform in dental office, promoting decontamination, improving healing and decreasing discomfort of patient is attractive. In our study we found that the 630nm diode lamp is safe and effective and reduce the time of healing of herpes simplex virus lesions.

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