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Review

Herpetic Lesions Affecting the Oral Cavity- Etiology, Diagnosis, Medication, and Laser Therapy: A Literature Review

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Abstract.

Oral herpetic lesions, primarily caused by the herpes simplex virus (HSV), present a significant therapeutic challenge due to their recurrent nature and impact on patient quality of life. After latency onset, HSV-1 can reactivate, causing frequent recurrences in some patients, while most individuals have few recurrences. Traditional treatment options for managing oral herpes include antiviral medications. These antiviral therapies function by inhibiting viral replication and alleviating symptoms, thus reducing the duration of lesions. These treatments have consistently demonstrated efficacy in reducing the duration and severity of lesions; however, their effectiveness can vary depending on the timing of administration, with early intervention yielding more favorable results.

In contrast, low-level laser therapy (LLLT) has emerged as a complementary treatment option, offering advantages in healing acceleration and pain reduction compared to antiviral treatments alone. Thus, this review aimed to explore the scientific literature that reported the treatment of herpetic lesions in the mouth with laser (Light Amplification by Stimulated Emission of Radiation) therapy. The most common clinical manifestation of HSV-1 is cold sores, affecting 40% of the world's population. It may be asymptomatic, but it usually has a high fever, aesthetic impairment, and painful oral lesions. It occurs initially as primary herpetic gingivostomatitis in children but can also affect adults who are still not exposed to the virus. Transmission occurs through secretions, oral droplets, or contact with symptomatic and asymptomatic lesions. Once an individual is infected with HSV, the infection may be recurrent as cold sores, with intermittent reactivations throughout life. Stress, systemic debility, sun exposure, and trauma are

important triggers of recurrent herpes. The infection is usually mild and self-limiting, and analgesia is sufficient. The patient's clinical history and physical examination are used to reach the diagnosis. The infection occurs more often in the reddened area and adjacent skin to the lips. The goal of this review was to revise the scientific literature involving the treatment of oral herpetic lesions with laser. There is no effective therapy to cure diseases caused by HSV-1, but there are several alternatives for its treatment. The treatment should be started as soon as possible, preferably at the onset of symptoms prodromal, no later than 48 hours after the onset of lesions. Since antiviral therapy does not prevent the recurrence of lesions and possibly causes viral resistance, low-level laser therapy intensity is a good alternative without side effects. When it is associated with a photosensitizing agent, through photodynamic therapy (PDT) or not, it minimizes established crises, relieves discomfort, and delays the appearance of new symptoms.

Keywords: cold sores; herpetic lesions; herpes simplex; low-level laser.

1. Introduction

Oral herpetic lesions manifest primarily as herpetic gingivostomatitis and recurrent herpes labialis (cold sores), each presenting unique challenges and implications for patient management. Herpetic gingivostomatitis often occurs as a primary herpes simplex virus (HSV) infection in children aged 6 months to 5 years. It is characterized by painful vesicular lesions affecting the gingivae, buccal mucosa, and sometimes the palate. The condition can lead to significant discomfort, affecting the ability to eat and speak effectively.[1] It can also affect adults not yet exposed to the virus.[2] They can also experience recurrent herpetic gingivostomatitis, particularly if they are immunocompromised or have previously encountered HSV. Painful lesions in the mouth and high fever are herpes symptoms.

Prodromal signs usually accompany the disease, but it may also be asymptomatic. Transmission usually occurs through direct contact, either through oral secretions and droplets or with symptomatic and asymptomatic lesions. Once infected with HSV, it may recur as cold sores, with intermittent reactivations throughout life. Burning and itching are symptoms of virus reactivation, followed by blisters. Lesions develop most frequently on the lip, perioral region, and hard palate. Physical or emotional stress, systemic impairment, sun exposure, and trauma are important triggers for recurrent herpes. The infection is usually mild and self-limiting, and analgesia is considered sufficient.[3-6] Recurrent herpes labialis (cold sores) typically occurs at the vermilion border of the lips due to reactivation of latent HSV-1. Cold sores present as painful, grouped vesicles that eventually rupture and crust over, often accompanied by prodromal symptoms such as tingling or burning.[7] Antiviral medications like acyclovir can diminish healing time and alleviate symptoms when taken at the onset of an outbreak.[8] While topical formulations are also available, their effectiveness can vary; studies suggest that topical acyclovir reduces healing time by approximately half a day compared to no treatment.[9] Given their frequency and impact, effective management strategies are crucial for those who suffer recurrent episodes.

For clinical application, therapeutic laser,[10-12] low-level diode laser, has been used to treat various pathological diseases in routine clinical procedures, ranging from recurrent aphthous stomatitis, mucositis, dentin sensitivity, traumatic ulcers, and temporomandibular dysfunction

(TMD), burning mouth syndrome, and viral infections, for the treatment of primary herpetic gingivostomatitis and recurrent herpes infection.[4,13]

Post-herpetic neuralgia (PHN) is a significant complication that can arise following the resolution of acute herpes simplex virus infections, including oral lesions. PHN is characterized by persistent pain in the area previously affected by herpes lesions and can linger long after the lesions have healed, significantly impacting quality of life.[14] The pathophysiology behind PHN involves nerve injury associated with the herpes infection, leading to neuropathic pain that may require specific treatments such as anticonvulsants or analgesics.[15] Understanding the spectrum of oral herpetic lesions, their management, and the potential for complications like PHN is essential in providing comprehensive care to affected individuals. Then, the goal of this review, observing a gap in the literature about a standardization of the laser (Light Amplification by Stimulated Emission of Radiation) application, was to explore the current scientific literature involving the treatment of herpetic lesions with laser therapy.

2. Materials and Methods

This comprehensive review, based on the outlined objective, was performed through the literature present in the online databases PubMed/MEDLINE, Google Scholar, and the Online Knowledge Library (B-On) without date restriction. The search terms used were: "Herpetic lesions", "Herpes", "LASER", "LASER therapy", "diagnosis", "medication", "drug", "treatment", "cold sore", "HSV", and "vaccine". Based on the aforementioned key terms, this study was developed.

The inclusion and exclusion criteria for the selection of articles that constituted the results of this study were: *Inclusion criteria*: (1) time frame: no restriction; (2) any clinical study; (3) language: English; and (4) studies reporting the treatment for the disease investigated. The exclusion criteria were: (1) without details about the treatment; (2) any revision or non-clinical study; and (3) lack of clarity for the diagnosis. Initially, the title and abstract of the articles found were evaluated; then, after duplication removal, the articles were screened via full-text reading, and finally, those that adhered to the eligibility criteria were included. The data analysis was carried out by four reviewers (ISSR, JSA, JEI, MRK), and the results obtained were discussed for all the authors.

3. Results

In the PubMed/MEDLINE and B-On, using the following combination: (Herpetic lesions) OR (Herpes)) AND (LASER)) OR (LASER therapy)) AND (diagnosis)) AND (medication)) OR (drug)) OR (treatment)) OR (vaccine)) AND (cold sore OR HSV), were respectively found 848 and 394 articles; and 1,710 results were found in the Google Scholar. After removing duplicates and those that did not fit the eligibility criteria, a total of 73 articles were followed for the next step

(full-text reading). Then, a total of 38 articles were included, which were part of the references of this study.

3.1. Herpes

3.1.1. Etiology

Herpesvirus, which belongs to the *Herpesviridae* family, is known to cause long-term infections in humans, initially characterized as primary herpetic gingivostomatitis and pharyngitis. Primary HSV-1 infection usually occurs in early childhood, from 6 months to 5 years. Still, it can also affect adolescents and adults, causing high fever and painful lesions throughout the oral mucosa during the acute phase. Saliva and occasional contact with herpetic lesions are the primary forms of virus transmission. When reactivated, recurrent lesions manifest as recurrent labial herpes with intraoral ulcerations on the mucosa, mouth, and skin.[3-6]

The most common clinical manifestation of HSV-1 is cold sores, causing pain and aesthetic impairment and affecting 40% of the world population.[16-18] Most oral infections are caused by HSV-1, such as ocular and facial infections, since this virus has a tropism for the oral epithelium. HSV-2 causes genital infections, but orogenital contact can cause infections of both types in the oral and genital mucosa, including concomitant infections.[3,6] They are characterized by forming small vesicles that come together and rupture, forming excruciating ulcers that evolve into crusts and scaling until they disappear entirely. For many, relapse is merely a painful and rapidly developing inconvenience; however, for immunosuppressed patients, e.g., those with HIV, this infection is associated with higher levels of morbidity and mortality, often under the conditions of an opportunistic agent.[6,17,18]

Herpetic gingivostomatitis is a primary infection caused by HSV-1, although HSV-2 can also be involved. This condition is particularly prevalent in young children and presents with painful vesicular lesions affecting the gingiva, buccal mucosa, and sometimes the throat. Patients may experience fever, irritability, and difficulty swallowing due to the inflammation and discomfort associated with the lesions. The vesicles typically rupture, leading to ulcerative lesions that can take up to two weeks to heal. The management of herpetic gingivostomatitis often involves supportive care, such as analgesics and hydration, while antiviral medications like acyclovir may be prescribed to reduce the duration and severity of the symptoms.[19] Both types of the virus can remain dormant in the sensory ganglia of the host and may be reactivated due to various triggers such as stress, illness, or immunosuppression.[20] The lifetime prevalence of HSV-1 is significant, with an estimated 67% of the global population being seropositive, while HSV-2 affects approximately 13%.[21]

In addition to the clinical manifestations, primary HSV infections can lead to complications, including PHN, a condition characterized by chronic pain in the areas previously affected by herpes lesions.[22] PHN can significantly impact the quality of life, causing long-lasting discomfort even

after the visible symptoms of an HSV infection have resolved.[23] The management of PHN often requires a multidisciplinary approach, including antiviral therapies and pain management strategies, to improve patient outcomes.[24] Understanding the nuances of herpetic gingivostomatitis and primary HSV infections is essential for timely diagnosis and effective treatment, reducing these viral infections' immediate and long-term impacts on individuals.

3.1.2. Epidemiology

Contact with oral secretions in childhood is the main reason for acquiring HSV-1. Nearly 90% of the world's population can be positive for HSV-1 by age 35; reactivation as cold sores is expected in half of those infected with the virus. The infection is evenly distributed across genders and ethnicities and has not yet been shown to have a specific geographic or seasonal distribution.[6] The virus is highly contagious, especially during the vesicle stage when its liquid contains millions of viral particles. Therefore, the dentist should temporarily suspend elective treatments when the patient is in this phase since the aerosol emitted during treatment becomes a risk factor for transmission.[25]

3.1.3. Pathophysiology and Histopathology

Both HSV-1 and HSV-2 exhibit significant virulence, latency, and reactivation. Neurovirulence is the ability of the virus to invade and replicate in the nervous system, and latency is the ability to maintain a latent infection in neurons. Reactivation is the ability to replicate and re-trigger the disease process induced by a specific stimulus.[3,5,6]

Once inside the cell, the virus replicates, penetrates the peripheral sensory nerves, and migrates through the axons to the regional sensory ganglia (trigeminal ganglion), where it remains latent until it is reactivated by triggers such as infections, excess UV radiation, stress, local trauma, hormonal changes during the menstrual period, immunosuppression and fever. The virus then migrates to the skin and/or mucosal cells, causing vesicular lesions, usually in the form of cold sores, which rupture and merge after about 2 days, forming ulcers covered by repair tissue (crusting phase). The rash is usually associated with tingling, burning, and discomfort, as well as nausea and fever.[3,5,6]

3.1.4. Cold Scores

The development of cold sores can be categorized into distinct stages, each characterized by specific symptoms and physiological changes during the course of an outbreak:

(1) Prodromal stage: the initial stage is marked by early warning signs, typically called prodromal symptoms. These may include tingling, itching, or burning sensations at the site where the cold sore will develop. This phase can last several hours to a day and signifies impending viral reactivation. Recognizing these prodromal symptoms is crucial, as initiating treatment during this stage can significantly reduce the severity and duration of the outbreak;[26,27]

(2) Vesicular stage: following the prodromal phase, the next stage involves the appearance of small, fluid-filled vesicles at the site. These vesicles are highly contagious and can be painful, often accompanied by inflammation and swelling of the surrounding skin.[27] The vesicular stage typically lasts from 24 to 48 hours, during which the lesions may merge and expand, creating larger areas of discomfort. Treatment initiated at this stage can still aid in alleviating symptoms and promoting quicker healing;[26]

(3) Ulcerative stage and Healing: after the vesicles rupture, they become ulcerated, forming shallow sores that crust over as they begin to heal. Depending on the individual's immune response and treatment, this stage can last anywhere from a few days to more than a week. During this period, secondary bacterial infection can occur if the lesions are not kept clean and covered.[28] Ultimately, the scabs will fall off as the skin heals, marking the outbreak's end. Maintaining hygiene vigilance during this stage is essential to prevent further infection or irritation.

Post-infection, individuals may experience PHN, characterized by persistent pain in the affected area long after the lesion has healed. This condition can affect the quality of life for some patients.[27] Also, the rationale for draining the gallbladder in the context of herpetic lesions is not a standard medical approach, as gallbladder drainage is typically reserved for cholecystitis or gallbladder obstruction resulting from gallstones or other complications. However, exploring the indirect connections between gallbladder health and viral infections such as herpes simplex can provide insight into why a thorough understanding of herpetic lesions and their complications might necessitate broader systemic evaluations in some patients. Herpetic infections, particularly those like herpetic gingivostomatitis, primarily affect the oral cavity and can lead to systemic complications if the virus spreads.

Some studies suggest that severe cases of HSV infections can result in complications like acute hepatitis, where the virus affects the liver tissue, potentially leading to symptoms that could mimic gallbladder-related issues. For instance, a case report indicates that viremia may occur in herpetic gingivostomatitis and is associated with the possibility of disseminated infection, including acute hepatitis.[29] In such scenarios, the presence of gallbladder issues, such as an impacting gallstone or inflammatory process, could complicate the clinical scenario, making it essential to evaluate the gallbladder’s health through diagnostic imaging or surgical assessment if indicated.

Furthermore, the relationship between viral infections and potential secondary effects on liver and gallbladder function emphasizes the importance of monitoring systemic signs in patients with herpes simplex infections. In cases where gallbladder dysfunction is identified alongside a herpes infection, drainage through percutaneous cholecystostomy or laparoscopic cholecystectomy may be warranted if the gallbladder is inflamed or infected. Treating such conditions is imperative to prevent further complications that could exacerbate the management of herpetic lesions, especially in immunocompromised patients or those with atypical presentations.[29] Even though

there is no direct rationale for routinely draining the gallbladder in cases of herpetic lesions, systemic evaluations may reveal complications that call for surgical intervention.

3.1.5. Diagnosis

The patient's clinical history and physical examination will define the diagnosis. Prodromal signs and symptoms, such as fever, irritation, burning, itching, pain, stinging, localized heat, or erythema in the affected epithelium, appear 6 to 24 hours before the development of lesions. The infection occurs most frequently in the reddened area and the skin adjacent to the lips. After this period, multiple small, erythematous, or yellowish papules and vesicles appear, which rupture approximately 2 to 5 mm in size, transforming into ulcerated lesions and presenting supportive symptoms. Scars form in two days, and healing occurs within 7 to 10 days in mild cases and 14 days in more severe cases. However, if necessary, it can be confirmed with complementary immunofluorescence tests by scraping the ulcerated lesions. Exfoliative cytology is also valid, as it confirms the diagnosis by containing Tzanck cells; however, it does not distinguish between HSV-1, HSV-2, and VZV (Varicella Zoster virus).[5,6,30]

It is important to define Tzanck cells or multinucleated giant cells; they are characteristic cytological findings in HSV infections, particularly those causing lesions like cold sores (herpes labialis) and herpetic gingivostomatitis. The Tzanck smear is a simple laboratory technique used to diagnose herpetic infections by scraping the base of a vesicular lesion to collect cells for microscopic examination. The presence of Tzanck cells on this smear suggests a herpes virus infection, as these cells demonstrate unique features such as multiple nuclei and changes in chromatin structure, including margination and molding of the nuclei due to the viral replication process.[31] The Tzanck smear has shown varying sensitivity and specificity in detecting herpes simplex infections. While the sensitivity can range from as low as 40% to as high as 80%, the specificity for identifying HSV can be up to 100%.[32] This technique is advantageous because it is rapid and cost-effective, allowing quick diagnostic results in acute clinical settings. However, multiple studies indicate that the Tzanck smear should not be relied upon exclusively for definitive diagnosis due to its limitations, specifically, its inability to differentiate between HSV-1 and HSV-2 and the high likelihood of false-positive results associated with various other conditions that also produce multinucleated giant cells.[33,34] Despite these limitations, the Tzanck smear remains a valuable diagnostic tool in specific contexts, particularly in resource-limited settings or situations where immediate pathology results are needed. Its rapidity can facilitate prompt treatment initiation, which is critical in managing herpetic infections effectively and preventing complications such as PHN.[35] Moreover, alternative diagnostic methods, such as polymerase chain reaction (PCR) and viral cultures, have increasingly taken precedence due to higher sensitivity and specificity. Still, they may not offer the same speed of turnaround as the Tzanck smear.[36] Thus, while Tzanck cells and the associated smear tests are valuable, they are generally employed with other diagnostic approaches to ensure accurate and timely management of HSV infections.

3.1.6. Differential diagnosis

Attention to the patient's age, group, and medical history is essential. Some conditions to differentiate are: Herpes Zoster (unilateral infection along the nervous system; usually in middle-aged and elderly people; painful blisters and ulcers); Chickenpox (associated with rashes, some blisters, and ulcers in the mouth; usually in children); Behçet's disease/syndrome (three-part ulcers; genital ulcers, and ocular inflammation); Cold sores (very painful, may be single or multiple; non-keratinized mobile mucosa; often recurrent); Erythema multiforme (predominantly in children and young adults; multiple vesicles and/or blisters and ulcers; presence of crusts; hemorrhagic lesions on the lips; may often be associated with "target" lesions on the skin or involvement of the genital and ocular mucosa; Stevens-Johnson syndrome); Necrotizing gingivostomatitis (painful destruction of the gingival papillae; bad odor; more common in adolescents and young adults); Cytomegalovirus ulcer (petechiae on the soft palate); Traumatic ulcer (mild to moderate pain, history of local trauma); Vesiculobullous diseases (lichen planus, pemphigus, pemphigoid , lupus, sarcoidosis. Usually more frequent in the elderly, the appearance of “squamous gingivitis”; red or white patches, macules or papules, vesicles, and/or blisters and ulcers precede the skin lesions; and Physical, chemical, and thermal injuries (local trauma, thermal or chemical burns).[6,37]

3.1.7. Treatment and Management

Gingivostomatitis is usually mild and self-limiting. The episode usually lasts between 7 and 10 days and heals completely, without intervention, within 21 days.[5,6] During the active phase of the infection, patients are prescribed petroleum jelly-based lip creams. Analgesics and oral solutions provide comfort and allow fluid intake. Staying hydrated during herpes treatment is essential.[5,6] Once the infection is resolved, the virus returns to the trigeminal ganglion; then, it remains latent until one of the causative agents is present and triggers a new infection.[5] However, it is crucial to guide and inform patients and family members about the progression of the disease, its mild and self-limiting nature, pain control strategies, hydration, and a balanced diet.[6] However, to date, there is no effective therapy to cure infections caused by HSV-1, but there are several alternatives for its treatment.[17,18]

3.1.7.1. Acyclovir

Antiviral therapy aims to reduce discomfort and pain, as well as to hasten remission of infection and reduce viral shedding. Treatment should preferably be started at the onset of prodromal symptoms and no later than 48 hours.[38]

Nucleotide analogs such as acyclovir, valacyclovir, and penciclovir are used to treat herpes infections. Several studies suggested topical acyclovir (cream) for sporadic lesions or oral suspension in mouthwash, including ingestion. For recurrent episodes (6 or more times per year), systemic use of oral acyclovir is indicated.[6,38,39] Antiviral treatment with acyclovir is the gold standard and the most widely used for preventing or suppressing HSV, but its continued use can cause viral resistance. It also has no preventive action on the recurrence of lesions.[6,18]

3.1.7.2. Vaccines

Vaccines are being tested for treatment and prevention, but none have proven completely effective. Generally, prophylactic treatment of these lesions is done with the topical and systemic use of Acyclovir, which aims to minimize the appearance of crises and alleviate symptoms. Otherwise, it can be responsible for viral resistance, and its use cannot prevent the recurrence of lesions.[17,18,40,41]

3.1.7.3. Low-level laser therapy (LLLT)

Laser (Light Amplification by Stimulated Emission of Radiation) is an electromagnetic reaction, a monochromatic, collimated, and intense light source, designed by Albert Einstein in 1917, used to promote cellular biostimulation. High-power lasers are used for surgeries with coagulation and tissue-cutting functions. If the power is low, it is generally applied to repair the tissue.[10,11,16,40] Recently, the therapeutic use of low-level laser (LLLT) or soft lasers has been proposed in health sciences as an alternative treatment in the management of recurrent labial herpes without side effects associated with a photosensitizing agent through antimicrobial photodynamic therapy (aPDT).[5,18]

Methylene blue is a safe and effective photosensitizer for aPDT, as it can inactivate coated and uncoated viruses. It acts specifically by damaging viral DNA; then, using methylene blue with a low-power red laser can fragment viral DNA. Moreover, PDT treatment does not have side effects, which is positive.[25]

For clinical application purposes, therapeutic laser, low-level diode laser, has been used in the treatment of several pathological processes or routine practical clinical procedures, ranging from traumatic ulcers, TMD, oral burning syndrome, candidiasis, post-chemotherapy or radiotherapy mucositis and, among viral infections, for the treatment of primary herpetic gingivostomatitis and recurrent herpetic infection, improving these inflammatory processes with edema reduction and analgesia.[3,16]

Since administering an antiviral drug cannot prevent the recurrence of lesions and can cause viral resistance, an alternative strategy to treat herpetic lesions is using PDT. It acts as an adjuvant to treat labial herpes, presenting a rapid reduction of the recurrence of lesions and wounds, simple and painless, providing satisfaction and comfort, and promoting a better quality of life.[4,18,40]

Table 1. Comparison of antiviral treatment and laser therapy for herpes.

	Antiviral	LASER
Onset time[42-46] Both treatments require early intervention for optimum effectiveness	Administered at the first sign of symptom onset (most effective); initiating antiviral therapy within 72 hours of the onset of symptoms significantly reduces the duration and severity of outbreaks	Aims to be effective at the vesicle stage, achieving symptom relief and reduced healing times
Recurrence prevention[46-48]	Antiviral agents can be used in an episodic or suppressive approach. For recurrent infections, it is suggested that episodic treatments significantly decrease the frequency of recurrences when patients self-initiate therapy at prodromal signs	It has potential reduction in the recurrence of herpes lesions through its mechanisms, suggesting long-term suppression after multiple treatments It may not achieve the same statistically significant reductions as long-term antiviral regimens
Side effects[45,49,50]	• Mild: gastrointestinal discomfort • Severe: renal toxicity and hematological issues, particularly with intravenous forms	• Minimal side effects: primarily localized discomfort during the procedure, which is often well-tolerated by patients • Relative non-invasiveness and painlessness, allowing usage in sensitive populations such as children

Then, the question is: how can local irradiation lead to a progressive reduction in a cutaneous infection of the ganglionic nervous system, and its effect persist for a year?[30,39] The LLLT produces an analgesic effect in the irradiated area, interfering with the electrical message at a local level, inhibiting the transmission of painful stimuli, balancing the resting membrane potential, promoting fibrinolysis, and interacting in the wound repair process, acting as an anti-inflammatory and analgesic. Combined with its biostimulant power, these properties reduce discomfort immediately after the first application and accelerate repair.[17]

The primary mechanism of aPDT treatment is to remove the vesicle fluid containing viral particles immediately. It is associated with the photosensitizer's oxidative potential at a specific wavelength, which occurs after light absorption. One safe and effective photosensitizer is methylene blue; it inactivates both enveloped and non-enveloped viruses. Combined with red laser light, they can fragment viral DNA without side effects.[16,25]

Among the effects mentioned, it is possible to include the acceleration of the bone sedimentation process,[10,11] as well as the degranulation of mast cells, in addition to promoting increased peripheral circulation, vasodilation, and proliferation of fibroblasts. As a biomodulatory

agent of cytoplasmic organelles, its main target is the lysosomes and mitochondria, initially acting as a stimulator of cell membrane regulation, subsequently triggering a series of reactions in the mitochondrial respiratory chain through the chemical activation of enzymes, promoting changes in metabolism, that is, in biomodulation.[3] The LLLT protocol will depend on the stage of the disease, and there is a specific protocol for the prevention and treatment of cold sores in the treatment of herpetic lesions.[18,25,51]

Prevention with no injuries: there can be no injuries to prevent herpetic recurrence with LLLT. An infrared laser (780 nm and 70 MW) is used on the entire lip, labial commissure, chin, and wing of the nose. The energy of 1 joule per point will be applied for five seconds at each point, totaling, on average, sixty points. Ten applications are recommended, performed twice to thrice a week, depending on the patient's availability. It is important to follow up with the patient after completing the ten applications, and it is possible to perform this protocol again after six months.[18,25,51]

Stages of recurrent cold sore lesions: in cases of recurrent lesions, the protocol varies according to the stage of the disease in which the patient is found.[18,25,51]

Prodromal: it is the phase without clinical signs and is very rapid. According to the literature, there is a broad therapeutic window for this stage of herpes, but two protocols are most common: one with lower energy consumption and another through aPDT, which has higher energy consumption. In the point technique, a red laser is used only in the region where the patient reports discomfort. In the low-energy protocol, 1 joule is applied per point in a single session. In the case of aPDT, it is necessary to use a photosensitizing agent, usually 0.05% methylene blue. The energy offered is 5 joules per point in a single session.[18,25,51]

Macule and Papule: the macular phase is represented by redness; the papular phase is associated with the appearance of edema in the region. The protocol is the same as reported in the previous item.[18,25,51]

Vesicle: This is the phase of the most significant viral load and greatest virus proliferation. In this phase, using LLLT directly on the vesicle is contraindicated, as the virus will be stimulated. Drain all vesicles and then use aPDT. Drainage uses a gum needle placed horizontally to rupture the gallbladder and filter the fluid. Filter paper blots the fluid, which contains a large amount of virus. This process is repeated until all the gallbladders have been drained. After drainage, 0.05% methylene blue is applied to the cotton-wool area for 5 minutes, pre-irradiation time. LLLT - 100MW - with a red wavelength is applied with an energy of 3 to 5 joules per point. A single session is recommended, but the protocol should be repeated if some vesicles persist the next day.[18,25,51]

Last phase: there is no longer any proliferation of the virus, but there is still esthetic damage to the patient, and there may be edema. One joule (1J) is applied per point of the low-power red laser. In the presence of edema, a low-power infrared laser is used, which emits two joules per point around it. It is recommended to do this every day while there is edema.[18,25,51]

4. Discussion

Oral herpetic lesions, primarily caused by the herpes simplex virus (HSV), present a significant therapeutic challenge due to their recurrent nature and impact on patient quality of life. HSV-1 is the most common clinical manifestation of cold sores; after latency onset, HSV-1 can reactivate, causing frequent recurrences in some patients, while most individuals have few recurrences. However, in immunosuppressed and neonatal patients, herpetic lesions can cause severe systemic disease.[16] There is a high level of contamination by HSV-1. Dentists often discontinue treatment when a patient presents with viral blisters. Recurrence of herpetic lesions is a potential occupational hazard for dentists. From the clinical and patient perspectives, this fact lies down on the aerosol produced during treatment.[25,51] Then, dental treatment for patients with recurrent HSV-1 is problematic due to the risk of spreading the infection and contamination. During recurrent lesions, viral counts increase; thus, the dental team has a higher risk of exposure, mainly if the lesion is open or in exudative vesicles. Dentists are more exposed to contamination than the general population, and herpes simplex is more frequent among them. Thus, in order to keep an ideal and safe place to treat patients with cold sores effectively, it is necessary to promote decontamination, improve healing, and relieve patient discomfort, which is appealing.

Traditional treatment options for managing herpes simplex labialis (HSL) and oral herpes include antiviral medications such as acyclovir, valacyclovir, and topical agents like penciclovir (gold standard procedure). These antiviral therapies function by inhibiting viral replication and alleviating symptoms, thus reducing the duration of lesions.[52,53] However, they often fall short in preventing recurrences or providing rapid pain relief and healing during acute phases, necessitating alternative strategies for enhanced management. Lesions related to oral herpes are highly painful, causing discomfort and, sometimes, aesthetic impairment; there is uncertainty about the causes of recurrence. Acyclovir is commonly used to prevent or suppress HSV, but continued use may lead to viral resistance.[3] Since acyclovir via oral administration is generally prescribed for those who experience six recurrences or more within a year, those who experience fewer recurrences may rely solely on topical acyclovir. These individuals also experience pain and occasional social restrictions due to cosmetic impairment and may be highly uncomfortable with their wounds.

These treatments have consistently demonstrated efficacy in reducing the duration and severity of lesions during acute episodes.[8] However, their effectiveness can vary depending on the timing of administration, with early intervention yielding more favorable results.[54] In contrast, LLLT has emerged as a complementary treatment option, offering advantages in healing acceleration and pain reduction.[46] Clinical studies indicate that LLLT can significantly shorten healing times of herpetic lesions compared to antiviral treatments alone, and many patients report less discomfort during the healing process when laser therapy is incorporated.[55]

Research shows that LLLT can alleviate pain, accelerate healing,[6,7] and reduce lesion size by promoting tissue repair mechanisms.[48,56] For instance, a study highlighted the efficacy of a 780 nm gallium-aluminum-arsenide (GaAlAs) laser, which demonstrated a significant reduction in lesion

size and related inflammation when applied regularly.[56] Other findings corroborate that combining both high-intensity and low-intensity lasers in a single treatment protocol can provide synergistic benefits in effectively managing HSV infections.[57] Moreover, laser treatments are often well-tolerated and have minimal side effects compared to traditional pharmacological approaches, offering a promising avenue for long-term treatment. When performed by a qualified dentist, it is a safe treatment, as there is no aerosol release, so the infection does not spread. In the cases presented by Ramalho et al.,[51] aPDT reduced the infectious phase of the vesicles and, when associated with Acyclovir during the macular phase, inhibited the progression of the infection. The authors concluded that treating labial herpes in the macular and vesicular stages with aPDT using methylene blue as a photosensitizer is effective and safe without side effects.

LLLT has been used in the clinic to treat several other pathological occurrences, including mucositis that manifests as erythema, ulceration, hemorrhage, edema, and pain. Thereby, improvement in the patient's condition was observed due to cellular activity stimulation, releasing growth factors by macrophages, the proliferation of keratinocytes, population increase and degranulation of mast cells, and angiogenesis, which caused a rise in the acceleration of the wound healing process due, in part, to the reduction in the duration of acute inflammation, resulting in faster repair.[58] Since herpes simplex viruses cause a similar clinical picture, low-intensity lasers could act similarly.[4,18]

LLL irradiation has been considered a noninvasive and non-cytotoxic alternative to conventional acyclovir treatment for cold sores. The study by Donnarumma et al.[16] demonstrated that treatment with diode laser irradiation causes a drastic reduction in viral infection in keratinocytes, which are the primary cells of HSV-1 infection. The laser modulates the inflammatory process during infection and, by preventing viral replication, facilitates the host immune response. According to Ferreira et al.,[4] the daily clinical efficacy of LLLT, associated with conventional basic therapy, can improve the patient's clinical condition. Antiviral drugs are effective when patients use them to treat prodromal symptoms. Even though the optimal dosage of Acyclovir is unknown, it reduces the symptoms of infection and duration. Furthermore, acyclovir does not prevent the recurrence of infection. Therefore, aPDT is a promising treatment modality and an interesting alternative for herpetic lesions.[3,30,59]

Laser therapy associated with aPDT leads to a shorter time for healing and a shorter recurrence period. It can be considered a low-cost alternative if the patient presents viral resistance to the drug prescribed (Acyclovir); for immunosuppressed patients with many recurrences of herpetic lesions; for patients who cannot administer medication due to an alteration in the acyclovir metabolizing organ; and for healthy patients with frequent recurrences to reduce discomfort.[3,18] The aPDT acts to immediately remove vesicle fluid, which contains a large amount of viral particles associated with the photosensitizer's oxidative potential after light absorption.[18,51]

Laser Therapy vs Antiviral Treatments

The comparative effectiveness of laser therapy and traditional antiviral treatments has been the subject of various investigations. For instance, a study comparing LLLT with acyclovir cream found that patients receiving laser treatment exhibited faster healing and symptom relief.[46] Furthermore, LLLT has been noted for its potential to modulate inflammatory responses and promote faster tissue regeneration, factors critical to recovery from oral herpes lesions.[16] Nonetheless, antiviral treatment remains essential for some patients, especially those with recurrent outbreaks or those requiring rapid resolution of symptoms due to the immediate effectiveness of systemic antivirals.[8] Studies suggest that while laser therapy can alleviate symptoms and reduce healing time, its role is often seen as adjunctive to standard antiviral regimens, making combined treatment approaches more beneficial for many patients.[48]

Despite the promising results of laser therapy in managing oral herpes, challenges remain, particularly concerning the practical applicability of these technologies in everyday clinical settings. The accessibility of LLLT devices and the need for trained personnel can limit its implementation, while the potential for HSV reactivation post-therapy in susceptible individuals cannot be overlooked.[60] Therefore, while both treatment modalities have their merits, a carefully tailored approach that considers the specifics of each patient's condition seems most effective. Integrating laser therapy into the treatment regimens for oral herpes, alongside established antiviral therapies, offers the best chance for achieving optimal patient outcomes, balancing immediate relief and long-term recurrence management.[61,62]

However, there are considerations regarding the use of laser therapy, particularly concerning the risk of HSV reactivation post-treatment, as observed in some clinical contexts.[60] Understanding patient history related to previous herpes infections is crucial, especially when planning laser interventions, since acute trauma to the mucosal surface can provoke reactivation in susceptible individuals.[63] While LLLT presents advantages in enhancing healing and pain management, its use should ideally be complemented with antiviral pharmacotherapy to ensure comprehensive management, particularly for recurrent herpes infections.[64] Therefore, a multimodal approach that intertwines antiviral medications with laser therapy appears to be the most effective in providing immediate relief and long-term suppression of herpes simplex lesions.

Photoinactivation of the virus has shown great promise, offering significant potential and providing a safety record for use in other human methylene blue therapies.[51] Ramalho et al.[51] divided patients into 3 groups: (1) photodynamic therapy (aPDT), (2) topical application of acyclovir (AC); and (3) with aPDT + AC association. Of the 75 patients, those who underwent PDT had immediate benefits related to reducing lesions, edema, and tingling. They concluded that photobiomodulation during laser irradiation (PDT) was responsible for the favorable and lasting results for patients with recurrent cold sores.[25] According to Ajmal,[65] all groups studied showed improvement in the parameters studied. However, the topical therapy group with CA adjuvant to

aPDT showed a more significant improvement in pain reduction and pro-inflammatory markers compared to the topical acyclovir alone and photodynamic therapy (aPDT) group.

Table 2. Comparative treatment of herpesvirus infection between antiviral treatment and laser therapy.

Antiviral	LASER
Drugs such as acyclovir, valacyclovir, and famciclovir are commonly employed to inhibit viral replication and reduce the severity and duration of symptoms. • Acyclovir For the initial treatment of herpes labialis, acyclovir is usually administered at 400 mg orally three times a day for 7-10 days. The prompt initiation of acyclovir can reduce the pain and duration of symptoms associated with oral herpes lesions.[8] In the case of recurrent herpes labialis, the dosage is often 800 mg orally five times a day for 5 days. This higher dosage regimen is designed to accelerate healing and reduce the severity of outbreaks.[8] • Valacyclovir An effective alternative for managing oral herpes due to its superior bioavailability. For initial episodes, the standard dose is 1g orally twice a day for 7-10 days. This dosage facilitates effective suppression of the virus and alleviates symptoms more efficiently than several doses of acyclovir.[66] For recurrences, it can be prescribed at 500 mg orally twice daily for 3 days or 1g orally twice daily for 5 days. These regimens are aimed at reducing viral shedding and healing time.[67] • Famciclovir It is another option and is typically dosed as 250 mg orally three times daily for 7–10 days for initial outbreaks. Like valacyclovir, famciclovir is favored for its convenience and dosing schedule.[68] For recurring infections, the recommended dosage is 125 mg orally twice daily for 5 days or a higher dose of 1 g taken twice daily for 1 day. The latter is particularly beneficial in treating sudden, severe outbreaks.[8]	Modulate inflammatory responses and promote tissue repair through various biological mechanisms, which can accelerate the healing process and reduce discomfort associated with conditions. It is considered a potential adjunctive therapy particularly for symptomatic management, with no standard "dosage" per se but generally administered according to device manufacturer recommendations, focusing on parameters such as wavelength and duration.[48]

5. Conclusion

Although HSV infection has a rapid course, this agent is often associated with complications in treating systemically compromised patients, where other associated pathogens are common. There is currently no effective therapy against HSV-1, but existing treatments help minimize flare-ups, alleviate discomfort, and space out the appearance of new manifestations. However, low-level laser therapy (LLLT) appears to produce an analgesic effect in the irradiated area, reduce discomfort immediately after the first application, reduce the period of disease onset, and have the advantage of not causing viral resistance. Future clinical studies could compare the efficacy of the drug and LLLT in order to provide more scientific evidence.

Abbreviations

HSV	Herpes simplex virus
LLLT	Low-level laser therapy
PDT	Photodynamic therapy
TMD	Temporomandibular dysfunction
PHN	Post-herpetic neuralgia
aPDT	Antimicrobial photodynamic therapy

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