

Topical treatment of herpes simplex lesion by lavender cream

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ABSTRACT

Background: Herpes simplex virus is a common human pathogen that establishes life-long latent infections. The development of new antiviral drugs, especially herbal preparations remain desirable. Lavender has been shown to possess antibacterial, antifungal, antiviral actions.

This study was designed to compare the safety and efficacy of topical Lavender cream, acyclovir cream, with placebo for the treatment of herpes simplex labialis patients.

Patients and Methods: Randomized, double blind, placebo-controlled study for herpes simplex labialis treatment, a total of 75 enrolled patients divided to three groups and given study medications; group I: Lavender cream, group II: Acyclovir cream, group III: placebo, applied topically to the lesion three times daily for 5 days. Patient's responses to treatment were followed by clinical evaluation of healing time, size of the lesion and pain sensation, and safety of using the topical treatment. Patients assessed themselves the day of the scab fell off. They also graded, on a daily basis, their perception of relief from pain and the overall benefit from treatment. Also evaluating levels of the Immunoglobulin (IgG, IgE, IgM, IgA, and IgD) in the serum of herpes simplex labialis patients.

Results: Herpes simplex patients showed a significant reduction in the healing time, size of lesions, and significant pain relief from the first topical dose as a result of treatment with lavender cream associated with immunity state improvement.

Conclusions: Lavender cream is a new candidate as a safe and effective topical treatment for herpes simplex labialis lesions.

Key words: Lavender, herpes simplex labialis. (J Bagh Coll Dentistry 2012; 24(sp. Issue 1):70-76).

INTRODUCTION

Herpes labialis is a commonly occurring ailment ⁽¹⁾. Approximately one-third of all infected patients suffer relapses ⁽²⁾. It is a rash of the skin and mucous membranes (in particular, the lips) and is characterized by erythema and blisters that are preceded and accompanied by burning pain. It is a harmless but often annoying ailment in immunocompetent patients and it usually heals spontaneously within 10 days. Herpes labialis is contagious for individuals who have not been previously infected by the virus and for those with weakened immune systems (e.g., those with HIV infection or undergoing chemotherapy) ⁽³⁾. In addition, herpes labialis infection can result in genital herpes through orogenital contact ⁽⁴⁾.

Research has shown that while recurrences of infections are spontaneous, they are associated with various triggers such as physical or emotional stress, fever, exposure to ultraviolet light, nerve or tissue damage, immunosuppressant, heat, cold, menses, concurrent infection, and fatigue ⁽⁵⁾. Both herpes simplex type 1 and herpes simplex type 2 are responsible for primary oral herpes simplex infections, with HSV-1 accounting for 75 to 90 percent of the cases ⁽⁶⁾.

Immune system deficiencies that are subtler, but not necessarily associated with a serious disease, might also increase the risk of experiencing Herpes simplex infections. For that reason, a comprehensive prevention-and- treatment plan should include measures designed to enhance immune function ⁽⁷⁾.

The name lavender is derived from the Latin "lavare", which means to wash. The fragrant flowers were used in ancient Rome and North Africa to scent public baths and were carried by the Roman army for use as a disinfectant ⁽⁸⁾. "Lavenders" in Medieval and Renaissance times were used for the storage of laundry. The Ancient Egyptians are said to have used the flower in the Mummification process ⁽⁹⁾.

Several therapeutic effects of lavender, such as sedative, relaxant, carminative spasmolytic, antioxidant, antiviral and antibacterial activities as well as several gastrointestinal nervous and rheumatic disorders have been reported ⁽¹⁰⁻¹³⁾.

The aims of the present study was to compare the efficacy in healing of herpes simplex lesion, pain relief, and safety of topical Lavender cream, acyclovir cream, with placebo, also study the levels of immunoglobulins.

PATIENTS AND METHODS

This study was conducted in a double-blind technique randomized, placebo-controlled. 76 patients were participating in this study, 45 of them were female & the other 31 were males. The

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age varied between 15 to 45 yrs., patients were randomized to 3 groups; group I (G I): Lavender cream, group II (G II): Acyclovir cream, group III (G III): placebo, applied topically to the lesion three times daily for 5 days.

Inclusion criteria were; the patients should have a history of recurrent herpes simplex, not suffer from any chronic debilitating disease, and not receive any antibiotics or steroids medication. While exclusion criteria were; Pregnant & nursing mothers, patients with Known systemic diseases that may be associated with herpes simplex.

At the beginning of the study each patient was given enough information about the nature of the study to gain maximum cooperation.

Each patient was followed up regularly by daily inspection during the period of application of the tested medications to the lesion to determine the end point time of healing process, size of the lesion, and the degree of pain (by measuring visual analog scale VAS), in addition to the self assessment on a daily basis, their perception of relief from pain and the overall benefit from treatment. Also safety of using these studied topical treatment.

Preparation of the Formula: Cream base formula for topical application of Lavender was prepared according to B.P. (1997) ⁽¹⁴⁾, Placebo is a cream base free from active constituent. **Acyclovir cream** (Zovirax™, GlaxoWellcome) was used as a reference for comparison.

Blood Samples Collection: Five ml of venous blood was drawn from 50 patients who are treated with studied medications, after diagnosis and randomization, and before starting drug treatment as a pre-treatment sample, and after 5 days of treatment as post-treatment sample. Blood samples were left for clotting and then centrifuged for 15 minutes at 2000 rpm for separation of serum, which was kept frozen unless analysed immediately.

Determination of Serum Immunoglobulin: Determination of serum level of the Immunoglobulin (IgG, IgE, IgM, IgA, and IgD) was made using a ready-made kit for this purpose. Equal volumes of reference sera and test samples were added to wells in an agarose gel containing a monospecific antiserum. The samples diffused radially through this gel and the tested compound (antigen) being assayed as forming a precipitin ring with the monospecific antiserum; rings diameters were measured, and concentrations were determined using standard curve prepared for this purpose ⁽¹⁵⁾.

Statistical Analysis:

Statistical evaluation of data was performed utilizing Chi-square test, Student's t-test and ANOVA test to compare between means. Differences were considered significant at P values <0.05. SPSS computer program was used for this purpose.

RESULTS

Thirty-one of the 76 treated patients received topical lavender cream, 29 Acyclovir cream, and 16 were treated with the placebo. Mean age was 38, distribution of lesion in female more than males, and the number of lesion occurrence per year was 10. The patient characteristics and clinical data are shown in Table 1 by treatment groups.

Healing time (scab loss) occurred in a mean 4.1 ± 0.2 days for lavender treated group, 6.1 ± 0.5 days for acyclovir group, and 8.4 ± 1.5 days for placebo group. The difference observed for healing time between the treated groups and placebo was statistically significant ($P = 0.0001$), table (1).

There was a significant reduction of the size of lesions in lavender and Acyclovir treated groups compared to placebo, while there is no significance difference between G I and G II, the difference only in the time to healing, as showed in fig. (1).

This study showed a highly significant difference between G I and G II in pain score, VAS decreased significantly in lavender treated group from the first applied dose more than Acyclovir treated and placebo groups, ($P = 0.0002$), fig. (2).

This study showed a significant reduction in the serum levels of the immunoglobulins; IgG, IgE, IgM, IgA, and IgD compared to baseline levels in both Lavender and Acyclovir treated groups ($p = 0.001$), while placebo treated group did not showed any significant change among immunoglobulins level, table (2).

Patients ranked the benefit of their topical treatment on a daily basis and graded the overall benefit from the medications. The ranking was on a 1 to 10-index scale (1 = no benefit at all; 10 = very effective treatment). At the final visit there was a statistically significant difference in the benefit index for both Lavender and Acyclovir cream versus placebo for this subjective evaluation, Lavender index 9.2 ± 0.1 , Acyclovir index 8.5 ± 0.1 , and placebo index 5.3 ± 0.2 , ($P = 0.01$), table (1). There were no side effects detected from using the tested drugs in this study.

DISCUSSION

Infections with herpes simplex virus (HSV) recur despite high levels of neutralizing antibodies ^(16,17)

and apparent active virus-specific cellular immunity^(18, 19). Both humoral and cellular immunities have been shown to be important in preventing infections in experimental animals and humans.

Antiviral medications are a commonly prescribed treatment for HSV. Treatment with antiviral medications can help lesions heal faster during an initial outbreak, lessen the frequency and duration of symptoms during recurrences, reduce the frequency of outbreaks, and decrease viral shedding. Acyclovir is a specific inhibitor of HSV-1, HSV-2 virus replication, with little toxicity for host cells⁽²⁰⁾. It requires a virus encoded thymidine kinase (TK) for efficient intracellular activation, which accounts, in part, for its selectivity. However, resistance to this antiviral drug has already been reported^(21, 22).

Topical therapy offers the benefit of minimal systemic exposure of the patient to the agent, and a route of application for useful antiviral agents, which cannot be given by a systemic route because of toxicity or poor absorption. Topical acyclovir has poor skin penetration⁽²³⁾. There is no ideal topical treatment for herpes simplex labialis. The aim of this study was to search for new natural product scaffolds with potential antiviral activity and without harmful or side effects. This is the first study of using topical lavender cream for the treatment of Herpes simplex lesions.

The main chemical components of lavender oil are α -pinene, limonene, 1,8-cineole, cis-ocimene, trans-ocimene, 3-octanone, camphor, linalool, linalyl acetate, caryophyllene, terpinen-4-ol, eugenol and lavendulyl acetate⁽²⁴⁾. Following topical application of the essential oil of *L. angustifolia*, linalyl acetate and linalool can be detected in the blood within five minutes, peak at 19 minutes, and are cleared within 90 minutes^(25, 26). They can also be detected in the blood following inhalation of lavender oil^(27, 28) and in exhaled air following massage⁽²⁹⁾.

As the virus replicates and lyses epithelial cells, a vesicle forms that contains the released virus particles. The fluids that then fill the vesicle result from the immune reaction and the erythema that accompanies the virus replication. The dilation of the blood vessels allow for the accumulation of fluids and the migration of the immune cells to the vesicle. Lesions form as a result of destruction of epithelial cells either through the lytic cycle of the virus itself or through the immune response destroying infected cells. The lesion usually persists 7 to 10 days, but may continue for three to four weeks⁽³⁰⁾. Pain may persist after the skin is healed.

Oral Diagnosis

The results of this study indicated that lesion size areas decreased at a significantly greater rate among lavender treated patients with complete healing. In addition to the significant healing time reduction earlier than the other two tested groups.

It seems that lavender has an anti allergic effect on mast cell-mediated immediate-type allergic reactions, and some concentration-dependent inhibition impact on histamine release from the peritoneal mast cells in mice and rats⁽³¹⁾.

Lavender enhance Free radical scavenging activity and decrease the stress hormone, cortisol, which protects the body from oxidative stress⁽³²⁾. Coumarin found in *L. angustifolia*, and caryophyllene oxide have anti-inflammatory effects⁽³³⁾, while Rosmarinic acid, hydroxycinnamic acid, 1,8-cineole, and beta-pinene may contribute antioxidant activity to Lavender^(34, 35), this may be a mechanism of action that explains Lavender activity in re-epithelialization and healing process faster than other groups, in addition to its actions as anti-inflammatory, and immunity enhancer. Other mechanism of action is that the antiviral activity of essential oils may be due to the direct interaction with virions.

Concerning the fast pain relief in lavender group more than the other treated groups, is referred to the lavender active constituents; linalool is the major pharmacologically active constituent involved in the anti-anxiety effect of lavender oil⁽³⁶⁾, Eugenol has local anesthetic effect^(37, 38), and Linalyl acetate and linalool have sedative and local anesthetic effects⁽³⁹⁻⁴¹⁾.

In Herpes simplex patients, antibodies to HSV are mostly IgG, although HSV-specific IgA is also detectable^(42,44). All the observations about the possible role of IgG, IgM, IgA and the complement protein components (especially C3) augment the concept of occurrences of immune complex vasculitis that is found essential step in the pathogenesis of oral ulceration⁽⁴⁵⁾. When immunofluorescence microscopic techniques are used to identify Immunoglobulins and complement components in the oral biopsy specimens of oral ulcers, the results revealed that circulating immune complexes might play a role in the damage produced during the course of disease⁽⁴⁶⁾.

Serum IgD was considered an early marker of B-cell activation⁽⁴⁷⁾. IgD can have a regulatory role, e.g., to enhance a protective antibody response of the IgM, IgG, or IgA isotype, or to interfere with viral replication⁽⁴⁸⁾. IgD was increased (100 U/ml) in many children with periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome⁽⁴⁹⁾. Lavender significantly reduced IgE-induced histamine release and tumor necrosis factor-alpha in a dose-dependent manner⁽⁵⁰⁾.

The results presented in this study concerning the changes in the levels of serum Immunoglobulins (IgG, IgE, IgM, IgA and

IgD) are compatible with some of the previously indicated studies, where significantly differences between pre- and post-treatment with topical Lavender cream were observed, compared to the other studied groups.

The findings of this study showed that healing process, reduced healing time, instant pain relief and enhance immunity among the lavender treated group was significantly better than the other studied groups. Treating Herpes lesions Naturally describes a safe and powerful natural remedy for such an infections.

The authors suggest to study the treatment of herpes simplex lesion caused by oxidative stress.

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Table 1: Patients' characteristics and clinical data by treatment groups:

Variables	G I: Lavender cream	G II: Acyclovir cream	G III: Placebo
No. of patients	31	29	16
Age (yr) *	35	36	38
Sex [female/ male]	19/12	16/13	8/8
Year with disease *	10	9	10
No. of lesion /yr	4	4	3
Family history (+ve/ -ve)	5/ 26	4/ 25	4/ 12
Location of lesion:			
Skin upper lip	6	5	1
Angle of mouth	7	8	3
Upper lip	9	9	6
Lower lip	9	7	6
No. of current lesions:			
Single	25	24	14
Double	6	5	2
Causes:			
Stress	18	14	6
Fever	13	15	10
Time to healing (days) **	4.1 ± 0.2	5.7 ± 0.5	8.4 ± 1.5
Rank index **	9.2 ± 0.1	8.5 ± 0.1	5.3 ± 0.2

Data expressed as number or as * mean, or as ** mean ± SD values.

Table 2: Serum immunoglobulins levels pre and post treatment in all studied groups:

Pre treatment	Ig G	Ig E	Ig M	Ig A	Ig D
G I: Lavender	1411.05±11	950±14	191.6 ± 2.4	266.2±12.2	937.4±12.2
G II: Acyclovir	1435±23	955±18	202.12±16	265.78±16.2	940.2±11.1
G III: Placebo	1465.5±15.2	945±16	207.6 ± 2.9	265.9±14	939.1±11.5
Post treatment					
G I: Lavender	340.45±11.8	158.4±0.2	162.4 ± 0.4	233.1±2.4	155.1±0.4
G II: Acyclovir	780±35.2	167.9±0.6	171.6±5.8	245.8±16.4	160.9±4.5
G III: Placebo	1465.56±15.2	945±17	207.68 ± 3.9	266.1±12.7	939.9±16.2

Data expressed as mean ± SD values.

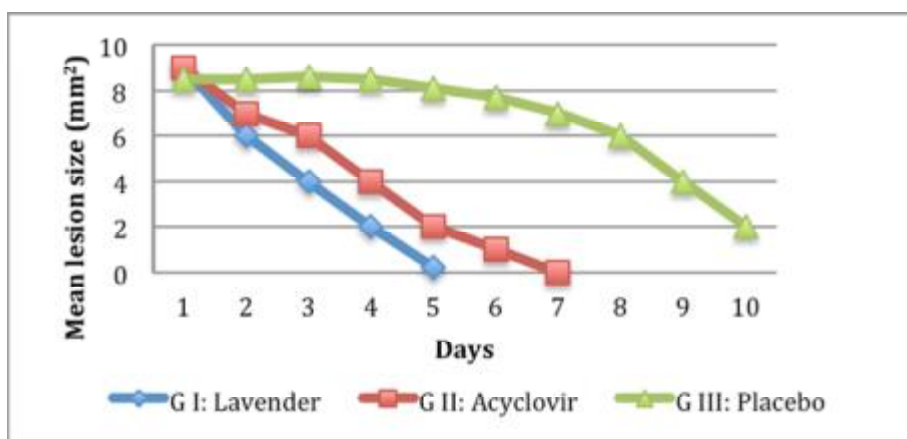


Figure 1: Mean lesion size (mm²) by days of the tested groups.

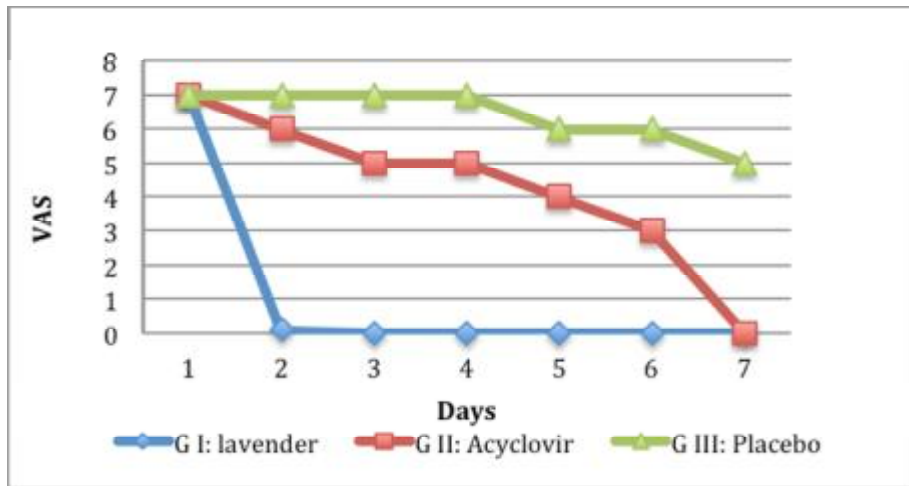


Figure 2: pain score (VAS) of the three groups by days. (Pain score: 1, none; 2, mild; 3, moderate; 4, severe).