Therapeutic Effect of Melissa Gel and 5% Acyclovir Cream in Recurrent Herpes labialis: A Double-Blind Randomized Clinical Trial

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Abstract

Background: Recurrent Herpes labialis (RHL), as a common herpes infection in healthy persons, is treated symptomatically. Melissa officinalis has antiviral effects may affect RHL.

Objectives: The current double-blind randomized study aimed to compare the clinical effect of Melissa gel and 5% acyclovir cream to treat RHL.

Materials and Methods: The current study was conducted on 60 healthy students of the faculty of dentistry and dormitory residents who had experienced RHL. Participants were randomly divided into group A (treated by Melissa gel) and group B (treated by 5% acyclovir cream). The subjects used the topical drugs for seven days; they were examined on the first, second, fourth and seventh days. Clinical parameters (size of lesion, pain severity, presence of erythema and healing time) were evaluated in each visit and their changes were recorded.

Results: There were no significant differences between the two groups considering the changes in the size of lesions, healing time and erythema around the lesion (except on the fourth day). Pain severity alterations among the two groups showed significant differences on the second and forth days.

Conclusions: Although Melissa gel effectively reduced pain severity on the second and forth days, it was not effective to treat RHL.

Keywords: Herpes labialis, Melissa, Acyclovir

1. Background

As a common form of Herpes Simplex Virus infection, Recurrent Herpes labialis (RHL) affects skin and vermilion borders of lips and is mentioned as cold sore. Its recurrence in some cases could be attributed to fever, menstruation, sun exposure and likely emotional stress. Lesions have a prodromal stage, which includes a tingling sensation followed by edema, clusters of vesicles and ulceration. Occasionally, the diameter of the lesions may be some centimeters associated with severe discomfort and extensive lesion (1). In healthy persons, recurrent HSV infection should be treated symptomatically and in some cases with several recurrences and painful or large lesions, professional intervention could be reasonable (2).

Many antiviral drugs such as acyclovir were intended to treat RHL to decrease the duration of lesions; although their therapeutic effects had been confined by the time of prescription, these agents could be effective only in the first few days of RHL (2, 3).

Recently many herbal preparations are suggested to treat these lesions by some researchers (4-9). Nowadays usual and available topical agents applied to treat RHL in Iran are 5% acyclovir cream and Melissa gel. Acyclovir has optimum therapeutic impression in prodromal phase (prevesicle formation phase) (2). Melissa gel, offered by Goldaru Pharmacy Co. in Iran, includes 1% gel based balm mint (Melissa officinalis) dried extract, standardized by 0.23% tannic acid. Melissa officinalis components are flavonoids of quercetin and rhamnocitrine, glycosides, phosphoric acid and tannins (especially 4% rosmarinic acid).

2. Objectives

Since these two agents (5% acyclovir cream and Melissa gel) are administered to treat RHL by clinicians in Iran and there was no controlled clinical trial to compare their efficacy, the current study aimed to compare the clinical effects of Melissa gel and 5% acyclovir cream to treat RHL.
3. Materials and Methods

3.1. Subjects and Experimental Protocol

In this double-blind randomized clinical trial, the subjects were healthy students of Yazd faculty of dentistry and dormitory residents with RHL from May 2010 to April 2011. The participants had a positive history for three recurrences of RHL (at least) in the previous year. Enrollment in the study was based on the following criteria:
1. Not to have systemic diseases or pathologic condition on the time of study
2. No drug consumption at all
3. No history of allergy
4. No history of recurrent aphthous ulcers

Participants with RHL who did not meet the criteria or were not available for follow up examinations were excluded from the study. The enrolled participants were briefed and then signed an informative consent. They were informed to refer to the Dep. of Oral Medicine in Yazd Shahid Sadoughi, faculty of dentistry, for drug administration by observation of any RHL prodromal phase symptoms such as tingling of lip or erythema.

In the first visit, after recording the demographic data, features of primary lesions (size of lesion, severity of pain and erythema around the lesion) were recorded by oral medicine specialist. Then, the participants were referred to the receptionist to get one of the encoded drugs based on random number table.

The sample size was decided according to similar studies (3, 10, 11), consultation with statistics specialists, considering the loss of samples, 75 subjects were selected and finally data of 60 subjects were analyzed.

The subjects were randomly divided into two groups of 30 subjects, by random number table:
- Group A used 5% acyclovir cream, and group B used Melissa gel. Usage instruction of drugs was explained to the ones who sought medical advice; thus a 0.24 inch (0.6 cm) strip of cream/gel was applied by rubbing on lesion site three times a day when awake for 7 days. Each subject was examined on the first, second, fourth and seventh days of starting the drug use, and alterations in pain severity, size of lesion, erythema and healing of lesion were monitored.

Pain severity was evaluated by visual analog scale (VAS) in every visit and compared with VAS in the first visit. (VAS is a 10 cm line that 0 is no pain and 10 is the most severe pain experienced by the patient) (12). Finally, each subject was questioned about any abnormal sensation in the area after using the drug and drug side effects.

The clinical parameters were evaluated for each subject on visits according to Table 1.

3.2. Topical Medications

Two topical drugs were used in the study: (a) 5% acyclovir (Topical Cream Acyclovir 5%, Pars Daru Co., Iran), (b) Melissa gel (Herbal Gel 5 gr, Goldaru Co., Iran) these drugs applied locally three times a day on the involved area.

The drugs were prepared by the pharmacist and were in similar containers and labeled with A or B sign. Subjects were unaware about the type of topical drugs.

3.3. Statistical Assessment

Data were analyzed by Mann-Whitney (pain alterations and size of lesion) and Chi-square (erythema and healing time) tests. SPSS statistical package version 13.0 was used for all statistical analyses. P values < 0.05 were considered statistically significant.

3.4. Ethical Consideration

Moral aspects of this study was confirmed in the Ethical Committee of Vice-Chancellor for Research of Shahid Sadoughi university of medical sciences (No. 4556, 4, 10, 2010) this research was registered by the Iranian clinical trials center (IRCT), No. 13870819442N1. All subjects signed an informed written consent before commencement of the study.

4. Results

There were 60 subjects, 14 males and 46 females, with the age range of 29 to 50 years, and a mean age of 31 years. There were 30 subjects in each group. The demographic characteristics of the subjects are listed in Table 2.

In first assessment, the mean and standard deviation values of VAS among group A were 1.7 and 2.27, and 0.86 and 1.25 for group B, respectively. Comparison of the pain severity alterations amongst the two groups showed significant differences on the second (P < 0.001) and fourth days (P = 0.002) (Table 3).

In the first assessment, the mean and standard deviation for extension of lesion were 19.80 and 12.07 (in square millimeters) for group A and 42.80 and 1.37 for group B, respectively. There were no significant differences regarding the changes in the lesion size between the two groups (P > 0.05); although, an impressive decrease was detected in Melissa gel group on the second day (P = 0.002) (Tables 4 and 5). There were no significant differences between the two groups according to erythema halo around the lesion except on the fourth day (Table 6) (P = 0.024); also, there were no differences in the number of healed subjects, and no one reported abnormal sensation and side effects in the area of drug application in the two groups (Table 7).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of lesion</td>
<td>Size of lesion assessed by a transparent grid calibrated to 1 mm²</td>
</tr>
<tr>
<td>Pain severity</td>
<td>Score of pain evaluated by VAS in every visit</td>
</tr>
<tr>
<td>Presence of erythema</td>
<td>Inflammation around the lesion, in case of erythema halo (+/-)</td>
</tr>
<tr>
<td>Healing of lesion</td>
<td>Days that were essential for crust formation and improvement of the symptoms</td>
</tr>
</tbody>
</table>

Abbreviation: VAS, Visual Analog Scale.
Table 2. Demographic Characteristic of the Subjects<sup>a</sup>

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Group A (n = 30)</th>
<th>Group B (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.10 ± 14.65</td>
<td>30.08 ± 12.06</td>
</tr>
<tr>
<td>Male</td>
<td>8 (26.6)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Female</td>
<td>22 (73.33)</td>
<td>24 (80)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values are presented as mean ± SD or No. (%).

Table 3. Comparison of the Pain Severity in the Two Groups<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Visual Analog Scale</th>
<th>5% Acyclovir Cream</th>
<th>Melissa Gel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.71 ± 2.27</td>
<td>0.86 ± 1.25</td>
<td>0.176</td>
</tr>
<tr>
<td>2</td>
<td>1.62 ± 2.11</td>
<td>0.37 ± 0.83</td>
<td>0.0001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>0.79 ± 1.36</td>
<td>0.10 ± 0.40</td>
<td>0.002&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>0.20 ± 0.60</td>
<td>0</td>
<td>0.116</td>
</tr>
</tbody>
</table>

<sup>a</sup>VAS 1, 2, 4 and 7 are pain severity on the first, second, fourth and seventh days.
<sup>b</sup>Values are presented as mean ± SD.
<sup>c</sup>P values < 0.05 were considered significant.

Table 4. Comparison of the Size of Lesion in the Two Groups<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Size of Lesion, mm&lt;sup&gt;c&lt;/sup&gt;</th>
<th>5% Acyclovir Cream</th>
<th>Melissa Gel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>19.80 ± 12.07</td>
<td>42.80 ± 61.37</td>
<td>0.116</td>
</tr>
<tr>
<td>S2</td>
<td>17.33 ± 12.00</td>
<td>29.67 ± 52.86</td>
<td>0.795</td>
</tr>
<tr>
<td>S4</td>
<td>10.50 ± 7.82</td>
<td>17.37 ± 35.87</td>
<td>0.322</td>
</tr>
<tr>
<td>S7</td>
<td>2.63 ± 3.85</td>
<td>7.27 ± 19.20</td>
<td>0.741</td>
</tr>
</tbody>
</table>

<sup>a</sup>S1, 2, 4 and 7 are size of lesion on the first, second, fourth and seventh days.
<sup>b</sup>Values are presented as mean ± SD.
<sup>c</sup>P values < 0.05 were considered significant.

Table 5. Comparison of the Mean of Lesion Size Decrease in the Two Groups

<table>
<thead>
<tr>
<th>Decrease of Lesion Size, mm&lt;sup&gt;c&lt;/sup&gt;</th>
<th>5% Acyclovir Cream</th>
<th>Melissa Gel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second day</td>
<td>2.5 ± 0.48</td>
<td>11.1 ± 2.05</td>
<td>0.002&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fourth day</td>
<td>6.8 ± 1.06</td>
<td>12.4 ± 1.12</td>
<td>0.11</td>
</tr>
<tr>
<td>Seventh day</td>
<td>7.9 ± 1.95</td>
<td>10 ± 3.18</td>
<td>0.51</td>
</tr>
</tbody>
</table>

<sup>a</sup>P values < 0.05 were considered significant.

Table 6. Comparison of the Erythema around the Lesion<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Erythema</th>
<th>5% Acyclovir Cream</th>
<th>Melissa Gel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>24 (80)</td>
<td>21 (70)</td>
<td>0.371</td>
</tr>
<tr>
<td>2a</td>
<td>18 (60)</td>
<td>15 (50)</td>
<td>0.431</td>
</tr>
<tr>
<td>4a</td>
<td>6 (20)</td>
<td>0</td>
<td>0.024&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7a</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Erythema 1, 2, 4 and 7 are the erythema around the lesion on the first, second, fourth and seventh days.
<sup>b</sup>Values are presented as No. (%).
<sup>c</sup>P values < 0.05 were considered significant.

Table 7. Comparison of the Lesion Healing in the Two Groups<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Healing of Lesion</th>
<th>5% Acyclovir Cream</th>
<th>Melissa Gel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2</td>
<td>18 (60)</td>
<td>29 (96.7)</td>
<td>0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>H4</td>
<td>25 (83.3)</td>
<td>27 (90)</td>
<td>0.448</td>
</tr>
<tr>
<td>H7</td>
<td>14 (46.7)</td>
<td>16 (53.3)</td>
<td>0.606</td>
</tr>
</tbody>
</table>

<sup>a</sup>H2, 4 and 7 are healing of lesion on the second, fourth and seventh days.
<sup>b</sup>Values are presented as No. (%).
<sup>c</sup>P values < 0.05 were considered significant.
5. Discussion

RHL as a common form of HSV infection has increased in the recent two decades (1). Common anti-viral drugs such as acyclovir are effective in pre vesicular stage of lesions but ineffective with the progression of the lesions (2, 3, 13). Recently, some herbal preparations were prescribed to treat the RHL, and some of them had useful effects (1). Melissa gel, as a Melissa officinalis extract, is one of the herbal drugs commonly used in Iran, especially to treat RHL; thus, the current study compared the clinical efficacy of Melissa gel with that of 5% acyclovir cream to treat RHL.

Melissa gel, an extract of Melissa officinalis, is one of the most commonly used herbal preparations in Iran. Apparently, this herbal extract directly inactivates some viruses (9).

The Melissa oil affects the virus before absorption, but not after penetration of the host cell; thus, it has direct antiviral effect on herpes viruses. Since the lipophilic essence of lemon balm essential oil facilitates its absorption, Melissa officinalis might be proper for topical treatment of recurrent herpetic infections (10, 14).

Follow up studies showed that the antiviral effect of Melissa officinalis is attributed to its tannins (15) essential oil (14), non-phenolic compounds (16) and rosmarinic acid (5, 17, 18). It can restrain protein synthesis in vitro and this is attributed to its caffeine acid and other active polymerized products (16). Melissa extract inhibited HSV-1 binding to host cells dose dependently and rosmarinic acid was the cardinal contributor to the antiviral property of Melissa extracts (5).

In the current study, there were no differences between the two drugs according to the changes of lesions extension; although Melissa gel decreased the size of the lesions on the second, fourth and seventh days compared to that of the first visit, more effectively. Phenolic compounds and rosmarinic acid of Melissa officinalis may contribute to this effect. These findings were similar to those of the Koytchev et al. (6). Since the presented data (Table 4) were widespread, no significant differences were observed between the groups.

There were significant differences between the two agents in decreasing the pain severity, especially on the second and fourth days; hence, Melissa gel was more effective on the days that patient had the most severe discomfort. Koytchev et al. (6) and Saller et al. (11) showed decrease in pain and burning after consumption of Melissa officinalis extract, also Dimitrova et al. (1993) (17) reported that veridical effect of Melissa officinalis L. extract within three and six hours of application, as a sing of M 4 administered in MTC, the remaining extracts inactive the virus at the 12th and 24th hours (17).

There was no significant difference in decreasing the inflammation (erythema halo) around the lesions between the two drugs. Although, Melissa gel decreased erythema halo on the fourth day significantly, this may be due to the substances such as rosmarinic acid (5, 17), compatible with that of Koytchev et al. (6). On the other hand, Saller et al. (2001) (11) reported that acyclovir cream was more effective than sage cream in decreasing the erythema halo around the lesions. This diversity could be attributed to different compounds in the two drugs (sage cream and Melissa gel) Melissa gel and 5% acyclovir cream showed no differences in the healing time and there were no side effects or abnormal sensations in the subjects of the two groups.

According to the results of the current study, Melissa gel was more effective than acyclovir to decrease the pain severity on the second and fourth days of lesions appearance; however, their clinical efficacy to treat RHL were not different, thus more studies are recommended.

Acknowledgments

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Footnotes

Author’s Contributions: All authors contributed equally in search, sample collection, analysis of the study and write the manuscript.

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References

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