Original Article

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Comparison of the Effectiveness of Mellisan Gel and Acyclovir 5% Cream in the Improvement of Recurrent Herpes Labialis

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ABSTRACT

BACKGROUND AND OBJECTIVE: Recurrent herpes labialis is a common infection of the mouth area, caused by herpes simplex virus. This infection appears in the mucus or lip skin and is commonly known as oral herpes. The purpose of this study was to compare the effectiveness of Mellisan gel and acyclovir 5% cream in the improvement of recurrent herpes labialis.

METHODS: This double-blind clinical trial was conducted on 60 patients (14 men and 46 women), with the average age of 23.8 years (minimum of 20 and maximum of 32 years) and a prior history of recurrent herpes labialis three times a year. The previously-coded medicines were randomly distributed among patients. The subjects were asked to apply the cream or gel locally on the infected region three times a day, according to the manufacturer's instructions. All patients were examined within one, two, four and seven days after using the cream or gel to determine the changes in pain intensity, size of the ulcer, inflammation and recovery time. IRCT: 13870819144281.

FINDINGS: Mellisan gel and acyclovir cream were not significantly different in reducing the size of the ulcer, inflammation or the associated side-effects. Mellisan gel was accompanied by a significant reduction in pain intensity in patients on the second and fourth days of the examination (p=0.0001 and p=0.02, respectively). Moreover, on the second day, there was a significant difference in recovery (p=0.001).

CONCLUSION: The results of this study suggested that Mellisan gel is more effective than acyclovir cream in terms of pain reduction and recovery, whereas no significant difference was observed regarding the size of the ulcer or inflammation. Also, the administration of Mellisan gel and acyclovir cream was associated with no side-effects.

KEY WORDS: Recurrent Herpes Labialis, Acyclovir Cream, Mellisan Gel.

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Introduction

Recurrent herpes labialis (RHL) is a common infection of the mouth area, caused by herpes simplex virus. This infection appears in the mucus or lip skin and is commonly known as oral herpes. The rate of RHL recurrence has been estimated at 20-40%. This infection is accompanied by fever, menstruation, harsh sunlight and probably mental stress.RHL starts with itching or tingling in the infection site and continues with swelling, formation of small vesicular clusters and finally an ulcer in the infected region. Sometimes, these sores are a few centimeters in diameter and lead to pain and deformity (1-3).

RHL in healthy individuals can be treated as soon as the symptoms appear, whereas in those with frequent, painful recurrences, professional treatment is required (1-3). Various topical antiviral agents such as acyclovir (4-8), penciclovir (9) and docosanol have been suggested for the treatment of RHL to reduce the duration of this infection. However, the advantages of these agents in reducing recovery time seem limited (4-9). In fact, most antiviral agents have limited effects on RHL and are mostly accompanied by significant side-effects (10). Recently, various herbal products with significant effects have been used for the treatment of RHL (11-16).

Currently, acyclovir 5% cream (Zovirax) is the most available therapeutic agent for RHL in the pharmaceutical market of Iran. This cream is most effective when applied during the first stage of RHL, before the appearance of blisters. Moreover, herbal Mellisan gel, containing dried Melissa officinalis (1%) and tannic acid, is produced by Gol Darou Company (Iran) (17). Mellisan gel contains the extracts of Melissa officinalis, which is one of the most commonly used medicinal herbs. The components of Mellisan gel include the dried leaf extracts of Melissa officinalis (gel based, 1%), standardized on the basis of 0.23% tannic acid. Melissa Officinalis contains flavonoids such as quercitrin, rhamnocitrin, apigenin glycosides, kaempferol, quercetin, luteolin, phenolic acid, triterpenes, citronellal (volatile oil), geraniol, neral, sesquiterpenes (beta-caryophyllene) and tannins such as rosmarinic acid (up to 4%), caffeic acid and chlorogenic acid with glycosidic bonds (17). The existing oil in Mellisan gel affects the virus before penetrating into the host cells, and therefore, it is able to directly affect the virus. Also, based on the lipophilic properties of the oil in Mellisan gel, it is able to locally treat RHL (17). A wide range of approaches have been applied for the treatment of RHL (18); however, the development of chemical treatments is still limited. For instance, this virus can replicate inside the cells, as a result, therapeutic agents must differentiate between the activities of the virus and the host cell (10, 19). An increasing number of viruses have become resistant to acyclovir in recent years (20). If Mellisan gel exhibits superior properties to other agents, it can be used as an alternative option for the treatment of RHL. The purpose of this study was to compare the effects of Melissan gel and acyclovir 5% cream on the improvement of RHL.

Methods

This randomized, double-blinded, clinical trial was conducted on 60 (14 men and 46 women) students of dentistry at Yazd Dental School and dormitory residents, with the average age of 23.8 years (min=20 and max= 32 years) and a prior history of RHL (three times a year). Permission was obtained from the Ethics Committee of the University (code=4556) and the study was registered in IRCT (code=13870819144281). The subjects were asked to visit the Clinic of Oral Medicine, affiliated to the School of Dentistry at Shahid Sadoughi University of Yazd in case they witnessed any changes, indicating the recurrence of RHL (a tingling sensation or redness around the infection site).

The inclusion criteria were as follows: 1) a prior history of RHL; 2) absence of concurrent

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systematic diseases; 3) no history of allergies or recurrent canker sores; and 4) not using other medications simultaneously. Informed consents were obtained from all the participants. Demographic information was recorded in a questionnaire, and infection features such as the size of the ulcer, redness around the infection site, ulceration and pain intensity were recorded during the first visit.

Afterwards, to perform this double-blinded study, the patients were referred to the secretary of the ward to receive the medicines, which were coded by the pharmacist (i.e., A and B) and placed in similar containers (according to the randomized table). The patients were asked to apply the cream or gel locally on the infection site three times a day, according to the manufacturer's instructions so that a thin layer of the cream or gel would cover the wound. On the first day of administration, pain intensity was measured, using Visual Analogue Scale (VAS).

On the second, fourth and seventh days of evaluation, the subjects were examined to evaluate changes in the ulcer and the related symptoms. On the specified days, changes in pain intensity were recorded, using VAS and compared with the measurements on the first day. Overall, VAS consists of a horizontal line, 10 centimeters in length, with one end indicating no pain (0) and the other indicating maximum pain (10). To determine the changes in the size of the ulcer, two main diameters of the ulcer were measured by a transparent paper (in mm^2). During each examination, inflammation was evaluated based on the redness around the infection site.

Also, recovery time was determined and recorded in the questionnaire, based on the number of days required for the ulcer to recover. Overall, recovery refers to the formation of crust over the wound and lack of erythema around the infection site. The two study groups were divided into sub-groups on the day of inclusion in the study, based on ulcer formation (15 samples per group). Finally, 60 subjects were selected and classified in four groups: 1) using acyclovir cream without any ulcers; 2) using acyclovir cream with an ulcer in the infection site; 3) using Mellisan gel without any ulcers in the infection region; and 4) using Mellisan gel with an ulcer in the infection site. The evaluation of variables was performed by a specialist in oral medicine. Changes in ulcer size and pain intensity were analyzed by Mann-Whitney test. Also, erythema, unusual sensations around the infection site and recovery time were analyzed by Chi-square test. $p<0.05$ was considered statistically significant.

Results

The mean age of the subjects was 23.8±2.6 years, ranging between 20 and 32 years. The mean age of the participants was 23.7±2.64 and 24±2.9 years in Mellisan and acyclovir groups, respectively (2.34±23.2 years in the acyclovir group without an ulcer, 2.92±24.1 in the acyclovir group with an ulcer, 2.96±24.333 in the Mellisan group without an ulcer and 2.87±23.6 in the Mellisan group with an ulcer). The comparison of differences in the size of the ulcer between these four groups did not show a significant difference (table 1). However, the comparison of differences in pain intensity between these four groups showed a significant difference on days two and four of examination ($p=0.0002$ and $p=0.02$, respectively) (table 2).

The comparison of differences in inflammation between these four groups revealed no significant difference on days one, two and four of examination (table 3). Moreover, the comparison showed a significant difference in recovery time between the four groups on day two, unlike days four and seven ($p=0.005$ on day two) (table 4). Also, the four groups were not significantly different in terms of experiencing unusual sensations during cream/gel administration (table5).

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Table 1. The comparison of changes in the ulcer size, based on the examination day in the two groups (classified based on ulcer formation)

Groups \ Days		First Day Mean±SD		Second Day Mean±SD		Forth Day Mean±SD		Seventh Day Mean±SD	
Acyclovir	With ulcer	13.101±12.93	12.07±19.8	10.69±17.87	12.01±17.33	7.79±11.53	7.82±10.5	4.54±2.93	3.885±2.62
	Without ulcer	10.44±16.67		13.55±16.80		7.98±9.47		3.15±2.33	
Mellisan	With ulcer	36.02±33.33	61.37±42.8	19.83±19.27	52.87±29.67	11.40±10.33	35.88±17.36	4.88±2.87	19.20±7.27
	Without ulcer	79.44±52.27		71.86±40.07		49.49±24.40		26.43±11.67	
p-value		0.24	0.116	0.95	0.795	0.62	0.322	0.85	0.741

Table 2. The comparison of changes in mean pain intensity, based on the examination day in the two groups (classified based on ulcer formation)

Groups \ Mean pain intensity		First Day Mean±SD		Second Day Mean±SD		Forth Day Mean±SD		Seventh Day Mean±SD	
Acyclovir	With ulcer	2.70±1.98	2.27±1.70	2.40±1.91	2.11±1.62	1.61±0.93	1.36±0.79	0.11±0.05	0.60±0.19
	Without ulcer	1.81±1.41		1.81±1.33		1.10±0.65		0.81±0.33	
Mellisan	With ulcer	0.87±0.6	1.25±0.86	0.28±0.1	0.83±0.37	0	0.402±0.1	0	0
	Without ulcer	1.52±1.13		1.0±0.65		0.56±0.2		0	
p-value		0.42	0.176	0.002	0.0001	0.02	0.03	0.48	0.116

Table 3. The frequency of inflammation in the two groups (classified based on ulcer formation)

Inflammation \ Groups			Acyclovir	Mellisan	p-value
First day	With ulcer	With erythema	13(86.7)	12(80)	0.37
		Without erythema	2(13.3)	3(20)	
	Without ulcer	With erythema	11(73.3)	9(60)	
		Without erythema	4(26.7)	6(40)	
	Total		24(80)	21(70)	0.371
Second day	With ulcer	With erythema	10(66.7)	6(40)	0.50
		Without erythema	5(33.3)	9(60)	
	Without ulcer	With erythema	8(53.3)	9(60)	
		Without erythema	7(46.7)	6(40)	
	Total		18(60)	15(50)	0.436
Forth day	With ulcer	With erythema	3(20)	0(0)	0.08
		Without erythema	12(80)	15(100)	
	Without ulcer	With erythema	3(20)	0(0)	
		Without erythema	12(80)	15(100)	
	Total		6(20)	0(0)	0.024

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Table 4. The comparison of recovery time based on the examination day in the two groups (classified based on ulcer formation)

Groups	Recovery time in Second Day					Recovery time in Forth Day					Recovery time in Seventh Day				
	With ulcer		Without ulcer		Total	With ulcer		Without ulcer		Total	With ulcer		Without ulcer		Total
	+	-	+	-		+	-	+	-		+	-	+	-	
Acyclovir	10(66.7)	5(33.3)	8(53.3)	6(46.7)	18(60)	11(73.3)	4(26.7)	14(93.3)	1(6.7)	25(83.3)	8(53.3)	7(46.7)	6(40)	9(60)	14(46.7)
Mellisan	14(93.3)	1(6.7)	15(100)	0(0)	29(96.7)	13(86.7)	2(13.3)	14(93.3)	1(6.7)	27(90)	7(46.7)	8(53.3)	9(60)	6(40)	16(53.3)
p-value	0.005				0.001	0.326				0.448	0.721				0.606

Table 5. The comparison of unusual sensations around the infection site in the two groups (classified based on ulcer formation)

Group	Unusual sensations in Second Day					Unusual sensations in Forth Day					Unusual sensations in Seventh Day				
	With ulcer		Without ulcer		Total	With ulcer		Without ulcer		Total	With ulcer		Without ulcer		Total
	+	-	+	-		+	-	+	-		+	-	+	-	
Acyclovir	8(53.3)	7(46.7)	3(20)	12(80)	11(36.7)	5(33.3)	10(66.7)	0(0)	15(100)	5(16.7)	0(0)	15(100)	0(0)	15(100)	0(0)
Mellisan	2(13.3)	13(86.7)	4(26.7)	11(73.3)	6(20)	2(13.3)	13(86.7)	2(13.3)	13(86.7)	4(13.3)	2(13.3)	13(86.7)	0(0)	15(100)	2(6.7)
p-value	0.078				0.152	0.083				0.718	0.102				0.150

Discussion

In this study, Mellisan gel was more effective than acyclovir cream regarding pain reduction and recovery time, whereas no significant difference was observed between these two agents in terms of ulcer size or erythema reduction. The infected region significantly reduced in size in the acyclovir group without ulcers. However, this difference between the Mellisan gel and acyclovir groups was not statistically significant, which was consistent with the results reported by Spruance et al. (21) and Gilbert et al. (22).

This can be justified by the low number of subjects in each sub-group; also, in both studies, acyclovir was used in the early stage of infection.The comparison of changes in pain intensity showed a significant difference between the two groups on days two and four of examination. Therefore, it can be concluded that Mellisan gel was more effective than acyclovir cream in reducing pain on days when the patients experienced the highest level of pain; this can be related to the antimicrobial effect of rosmarinic acid found in Mellisan gel. These results were in accordance with the findings reported by Koytchev et al. (11) and Saller et al. (23). In studies by Spruance et al. (21) and Marrel et al. (24), use of acyclovir cream reduced pain in patients. In these studies, only acyclovir cream was used during the early stage of RHL. In the study by Saller et al. (23), the effect of acyclovir on decreasing erythema was more significant than sage cream during the first examination, which was in contrast with the findings reported in the present study. This can be due to differences in the properties of sage and Mellisa officinalis. In the present study, no side-effects were reported in the two groups. Mellisan gel was more effective than acyclovir cream on the second day of examination. The role of Mellisan gel in pain alleviation and erythema reduction on days two and four can be related to the presence of polyphenols in Mellisan gel (23). On the fourth day of examination, recovery in the acyclovir group

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without ulcers was greater than the acyclovir group with ulcers; this can be completely justified by the mechanism of acyclovir's effect. Moreover, the results reported by Koytchev et al. were in line with the findings of the present study (11)According to the present findings, Mellisan gel was more effective than acyclovir cream in reducing pain and recovery time, whereas no significant difference was observed in the size of ulcers or erythema reduction. Also, the administration of these compounds had no side-effects for the patients. According to the results, it is recommended that further studies with a larger sample size be performed to compare the effects of these two agents.

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