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ARAŞTIRMA / RESEARCH

Comparison of topical acyclovir and penciclovir in recurrent herpes labialis treatment

Rekürrent herpes labialisin tedavisinde topikal asiklovir ve pensiklovir etkinliklerinin karşılaştırılması

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Abstract

Purpose: The aim of this study is to compare the effects of acyclovir and penciclovir creams in the treatment of recurrent herpes labialis.
Materials and Methods: Seventy patients with pre-diagnosed recurrent herpes labialis lesions were enrolled in this study. Diagnosis was confirmed with HSV-1 IgM antibody test. Patients were separated under 2 treatment groups as acyclovir and penciclovir cream. Both agents were applied until complete healing of the lesions was seen. Burning, itching and bleeding scores; time of erythema, vesicles, ulceration, crusting and crust loss of the lesions were recorded. Pain values of the patients were recorded using a visual analog scale (VAS) and DASS-21 scale was used to measure emotional state related to depression, anxiety and stress.
Results: Pain level in the acyclovir group was significantly lower than the penciclovir group in the 3rd day, though with no difference in the following days. DASS-21 scores revealed signs of depression on 62.8% of the patients, anxiety on 34.2% of the patients, and stress on 41.4% of the patients in moderate or higher levels. While the pain level was higher in patients with high anxiety severity, it was observed that the pain level was low in patients with high stress intensity.
Conclusion: Although it is not possible to cure recurrent herpes labialis completely, any methods and drugs that shorten the healing time of the lesion and reduce pain and discomfort gains importance. Our study showed that acyclovir is superior in reducing pain.
Keywords:. Herpes simplex virus, recurrent herpes labialis, acyclovir, penciclovir

Öz

Giriş: Bu çalışmanın amacı, rekürrent herpes labialisin topikal tedavisinde asiklovir ve pensiklovir etken madde içeren kremlerin etkilerini karşılaştırmaktır.
Gereç ve Yöntem: Çalışmamıza rekürrent herpes labialis tanı konmuş lezyonu olan 70 hasta dahil edildi. Teşhis HSV-1 IgM antikor testi ile doğrulandı. Hastalar asiklovir ve pensiklovir etken maddesi içeren kremlerin kullanıldığı iki tedavi grubuna ayrıldı. Her iki ajan lezyonlarda tam iyileşme görülene kadar uygulandı. Yanma, kaşıntı ve kanama skorları; lezyonların kızarıklık, vezikül, ülserasyon, kabuklanma ve kabuk kaybı zamanları kaydedildi. Hastaların ağrı değerleri görsel analog skala (VAS) ile kaydedildi ve depresyon, anksiyete ve stres ile ilgili duygusal durumu ölçmek için DASS-21 skalası kullanıldı.
Bulgular: Asiklovir grubundaki ağrı düzeyi, sadece üçüncü günde pensiklovir grubuna göre anlamlı derecede düşüktü. DASS-21 skorları, hastaların %62,8'inde depresyon, %34,2'sinde anksiyete ve %41,4'ünde orta ve yüksek düzeyde stres belirtisi gösterdi. Anksiyete şiddeti yüksek hastalarda ağrı düzeyleri yüksek iken, stres yoğunluğu yüksek hastalarda ağrı düzeyinin düşük olduğu görüldü.
Sonuç: Rekürrent herpes labialisin tamamen tedavisi mümkün olmamakla birlikte lezyonun iyileşme süresini kısaltan, ağrı ve rahatsızlığı azaltan her türlü yöntem ve ilaç önem kazanmaktadır. Bu bağlamda çalışmamız, asiklovir etken madde içeren ajanın, ağrıyı azaltmada pensiklovir etken maddesi içeren ajana göre daha üstün olduğunu göstermiştir.

Anahtar kelimeler: Herpes simpleks virüs, rekürrent herpes labialis, asiklovir, pensiklovir

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INTRODUCTION

Herpes originates from the Greek word 'herpein', which means creep or crawling[1]. The definition of herpes, which is thought to be spread by creep, has been used to describe the wounds that develop and spread insidiously on the skin due to various reasons in the past. Currently, it is defined as self-healing vesicular lesions with the primary cause of Herpes Simplex Virus (HSV). HSV is a highly contagious virus that is transmitted through direct contact with infected body fluid[2]. Primary HSV infection occurs when antibodies passed from mother to child lose their protection. The virus remains latent in nerve cells in the body and, in cases where immunity is weakened, reactivates and causes recurrent infections.

While HSV's ability to cause infection was first shown in 1919, it was reported in 1930 that there were neutralizing antibodies against HSV in adults with recurrent herpetic lesions[3,4]. Herpes simplex virus-2 (HSV-2), one of the HSV infections with 2 subtypes, causes infections in the genital and anal area, while herpes simplex virus-1 (HSV-1), which affects approximately 67% of the population, causes infection in the skin and mucosa[2]. Recurrent Herpes Labialis (RHL) in the oral region is the most common of HSV-1 infections. Conditions that cause weakening of the immune system such as stress, cold, ultraviolet light, high fever, menstruation, trauma are important factors in the recurrence of lesions[5].

Viral titers peak within the first 24 hours after lesion formation, at which time most lesions are at the vesicle stage and then gradually decrease in the form of ulcers /crusts. Patients typically experience prodromal stage associated with itching, burning, and paresthesia before the appearance of erythema and papules. In some patients, the lesions are stopped or blocked and do not progress to the vesicle stage. Although self-limiting and benign, RHL is painful, long-lasting, and debilitating, and can significantly impair quality of life, especially in the vesicle and ulcer stages.

Before the lesions appear, symptoms such as pain, burning, itching, and paresthesia are observed at the lesion site. Lesions include erythema, papules, vesicles, pustules, ulcers and ultimately the sequential development of crusts[6]. In individuals who do not develop secondary bacterial infection and have a normal immune system, bursting of vesicles, crust development and recovery are completed within 7-10 days[5]. Recovery can occur spontaneously, but topical antiviral drugs are preferred as they reduce the virus load and contagiousness[5]. The use of antiviral drugs will also be helpful in reducing the severity of symptoms and the frequency of recurrence of lesions[7].

Antiviral agents used in the treatment of RHL are acyclovir, famciclovir, penciclovir and valaciclovir[6,8]. Of these agents, only acyclovir and penciclovir are suitable for use in topical form. Both compounds are analogs of the natural nucleoside deoxyguanosine. It is selectively phosphorylated by viral thymidine kinase only in virus-infected cells, resulting in termination of viral DNA synthesis by selective inhibition of viral DNA polymerase[9].

Although acyclovir and penciclovir have similar mechanisms of action, in vitro studies comparing these two agents showed significant intracellular pharmacodynamic differences[10]. Therefore, in our study, it was aimed to compare the effectiveness of these two agents on the symptomatic treatment of RHL.

MATERIALS AND METHODS

Our study has been approved by Gaziantep University Clinical Research Ethics Committee (Decision number: 2018/184) and Ministry of Health, Turkish Medicines and Medical Devices Agency (Decision number: 93189304-514.04.01-E.178530). In our study, all principles of the Declaration of Helsinki were followed, and the names and medical information of the patients were kept confidential during the study.

Sample

Our study was carried out on 70 volunteered patients with lesions who had pre-diagnosis of RHL and were admitted to Gaziantep University, Faculty of Dentistry, Oral and Maxillofacial Surgery Clinic. The patients were informed about the aim of the study, the treatment process and possible complications, and their written consents were obtained. Patients aged between 18-65, with RHL lesion and admitted to our clinic within the first 24 hours after the onset of symptoms, who did not have a disease affecting the immune system, and who could read and understand the consent form were included in the study. Patients with any immunosuppressive systemic disease, pregnant or suspected pregnancy, under 18

years of age, potentially exposed to chemicals or radiation due to their profession, previously undergone radiotherapy or chemotherapy, and unable to read and understand the consent form were excluded from the study.

Procedure

HSV-1 IgM antibody test was performed in patients with a clinical diagnosis of RHL. As a result of the positive response of the antibody test, the diagnosis was confirmed and the data of the patients were included in the study. The patients were called for follow-ups on the 1st,3rd, 5th and 7th days, provided that the treatment was started on the first day.

During the follow-ups, the burning, itching and bleeding scores (in the range of 0-5) were recorded. The time of erythema, vesicles, ulceration, crusting and crust loss of the lesions were recorded. At each follow-up, the pain values of the patients were recorded using a visual analog scale (VAS). Depression, Anxiety, Stress Scale (DASS-21) was used to measure emotional state related to depression, anxiety, and stress.

Measures

VAS

VAS is the simplest and commonly used instrument for measurement of psychometric responses that cannot be measured directly. It uses a 100 mm long line between two endpoints[11]. For pain assessment, a mark between 'no pain' and 'worst pain possible' points were used. Patients placed a single mark on the straight line that fits their pain level[12].

DASS-21

DASS-21 is a scale, evaluating depression, anxiety and stress factors, containing 7 items for each factor[13]. It was adapted to Turkish by Sarıçam having cronbach alpha internal consistency coefficients as 0.87 for depression subscale, 0.85 for anxiety subscale and 0.81 for stress subscale[14].

Treatment

Within the scope of the study, two treatment groups were formed; each consisting of 35 patients, using Zovirax 5% cream (GlaxoSmithKleine, London, UK) containing 50 mg acyclovir for 1 g or Vectavir 1% cream (Novartis, Basel, Switzerland) containing 10 mg penciclovir for 1 g. Each drug is available in 2 g packages. Patients were randomly assigned to one of these two treatment groups. MedCalc V 16.8.4, (MedCalc Software Ltd, Ostend, Belgium) program was used for randomization. This study was designed as an open-label trial therefore, after randomization, patients were aware of the treatment group they were allocated to.

Acyclovir 5% cream was used 5 times a day at approximately 4-hour intervals by skipping the night dose. Penciclovir 1% cream was applied at approximately two-hour intervals during the day (approximately 8 times a day). Both drug treatments lasted 4 days.

Statistical analysis

Normality test was performed using the Sapphiro Wilkes test. One Way ANOVA test was used for normally distributed data, Mann-Whitney U test for non-normally distributed data, and chi-square test for categorical data. The analyzes were made using the default packages in R 3.5.2 programming language (Ithaka and Gentleman, Auckland, New Zealand). The significance threshold value for the p value was determined as 0.05.

RESULTS

70 patients were included in the study; divided into 2 groups as acyclovir and penciclovir. The acyclovir group consisted of 19 female (54%) and 16 male (46%) with a mean age (SD) of 32.45 (± 10.26) years, the penciclovir group consisted of 16 female (46%) and 19 male (54%) with a mean age (SD) of 34.51 (± 10.54) years (Table 1). Age and gender distributions were similar in both groups. HSV-1 IgM antibody tests of all patients, included in the study, were positive.

Although the burning and itching symptoms decreased over time, the bleeding finding increased on the 5th day and then decreased. There was no significant difference between the symptoms of burning, itching and bleeding in both treatment groups ($p > 0.05$), except bleeding on 3rd day. Bleeding was thought to be related to the ulceration phase, but no significant relationship was found ($p > 0.05$), (Table 2).

Erythema and vesicle formation/ulceration stages were completed by the 3rd day in all patients. Following this phase, the days of crusting and loss of crust were compared, and no significant difference

was found between both treatment groups (p> 0.05), (Table 3).

Before starting treatment, there was no difference between the 2 groups in VAS-related pain levels. However, on the 3rd day, the pain level in the acyclovir group was significantly lower than the penciclovir group (p <0.001) (Figure 1). In the following days, it was observed that there was no difference between the groups in terms of pain levels (p> 0.05), (Table 4).

The emotional state of the patients was assessed using the Depression, Anxiety and Stress Scale (DASS-21) on 1st day of the study. DASS-21 scores revealed signs of depression on 62.8% of the patients, anxiety on 34.3% of the patients, and stress on 41.4% of the patients in moderate or higher levels (Table 5). Age and gender distributions of these findings were similar. When the effect of emotional state on RHL symptoms was examined, it was observed that patients with high depression severity had significantly higher itching symptoms (p = 0.006). However, there was no correlation between emotional state and burning, bleeding, crusting and crust loss times (p> 0.05). While there was no relationship between depression and pain, a significant relationship was found between pain and anxiety and stress. While the pain symptom was high in patients with high anxiety severity, it was observed that the pain symptom was low in patients with high stress intensity (p<0.05).

Table 1. Demographic characteristics of patient population by treatment group

	Gender		
	Female (%)	**Male (%)**	Age mean (± SD), y
Acyclovir	54	46	32.45 (± 10.26)
Penciclovir	46	54	34.51 (± 10.54)

SD: Standard deviation, y: Years

Table 2. Distribution of the symptoms between treatment groups

		Acyclovir mean (± SD)	**Penciclovir mean (± SD)**	**p value[1]**
Burning	1st day	1.48 (0.85)	1.54 (0.65)	0.905
	3rd day	0.31 (0.52)	0.48 (0.50)	0.114
	5th day	0.31 (0.79)	0.28 (0.45)	0.503
	7th day	0.02 (0.16)	0	0.317
Itching	1st day	1.20 (0.90)	1.14 (0.49)	0.765
	3rd day	0.34 (0.68)	0.45 (0.56)	0.184
	5th day	0.08 (0.28)	0.08 (0.28)	>0.999
	7th day	0	0.05 (0.33)	0.317
Bleeding	1st day	0	0	>0.999
	3rd day	0.08 (0.28)	0.42 (0.55)	0.002
	5th day	0.34 (0.48)	0.25 (0.50)	0.338
	7th day	0.05 (0.23)	0.14 (0.42)	0.383

[1]Mann-Whitney U test, SD: Standard deviation

Table 3. Relationship between phases of the lesion and treatment groups

	Acyclovir mean (± SD)	Penciclovir mean (± SD)	p value[1]
Erythema	1.05 (0.23)	1.00 (0.00)	0.493
Vesicles/Ulceration	2.48 (0.50)	2.57 (0.50)	0.632
Crusting	3.94 (0.72)	3.91 (0.61)	0.459
Crust loss	5.77 (0.73)	5.77 (0.80)	0.765

[1]Chi-square test, SD: Standard deviation

Table 4. Visual Analog Scale pain findings between treatment groups

	Acyclovir mean (± SD)	Penciclovir mean (± SD)	p value[1]
VAS/1st day	2.65 (0.99)	2.77 (0.84)	0.108
VAS/3rd day	0.31 (0.52)	1.17 (0.70)	<0.001
VAS/5th day	0.60 (1.37)	0.68 (0.71)	0.063
VAS/7th day	0.11 (0.52)	0.14 (0.35)	0.198

[1]Mann-Whitney U test, SD: Standard deviation

Table 5. Frequencies of depression, anxiety and stress obtained by DASS-21

	Depression (%)	Anxiety (%)	Stress (%)
Normal	15.7	45.7	28.6
Mild	21.4	20.0	30.0
Moderate	57.1	30.0	27.1
Severe	4.3	0	8.6
Extremely Severe	1.4	4.3	5.7

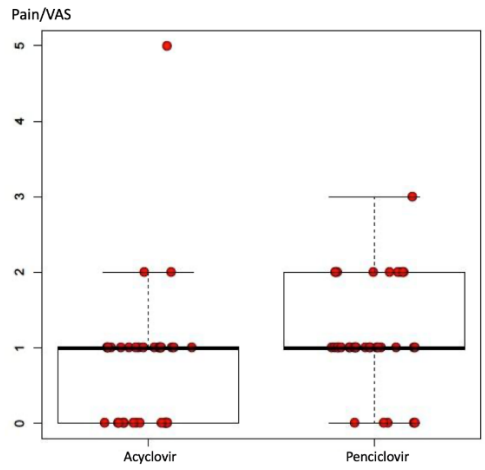

Figure 1. Visual analog scale pain findings on the 3rd day according to treatment groups.

DISCUSSION

RHL lesions can be diagnosed clinically. However, laboratory approval is required for the diagnosis to be confirmed. Although tissue culture and viral isolation are the most effective method for diagnosis, it may take a long time to obtain results[8]. Therefore, serological tests are preferred in recurrent lesions. We also used HSV-1 IgM antibody tests to confirm the diagnosis of RHL.

In addition to medical treatments such as zinc-containing creams, anesthetic creams, topical or oral antiviral drugs, non-invasive methods such as photodynamic therapy and low-level laser therapy are also used in the treatment of RHL[15]. Although photodynamic methods and low-level laser therapy are reported to alleviate the symptoms associated with RHL, these methods are uneconomical solutions due to device requirements and regular clinical visits. Among medical treatments, topical or oral antiviral drugs have been reported to be effective in relieving the symptoms of RHL and preventing recurrent lesions[15]. Although the use of antiviral drugs is safe and beneficial in the treatment of RHL, it is known that oral antiviral drugs cause side effects such as headache and nausea regardless of the dosage and duration of treatment[15]. Therefore, topical antiviral drugs were used in our study.

Today, the most important safe antivirals with specific antiviral effects and low toxicity in the treatment of herpes infection are acyclovir, famciclovir, penciclovir and valaciclovir[6]. Valaciclovir and famciclovir are suitable for systemic use only. Therefore, acyclovir and penciclovir, which are the only antivirals that can be prescribed for RHL in topical forms, were used in our study.

Our study showed that acyclovir significantly reduced pain on the 3rd day compared to penciclovir. Chen et al. reported that acyclovir shortened the time to resolution of pain compared to placebo, while Femiano et al. stated that in patients using penciclovir, the pain disappeared sooner than those using acyclovir[6,10]. Femiano et al. started treatment only after the formation of vesicles, which may explain the difference seen with our results.

It has been reported that the lesion healing time of penciclovir is similar to acyclovir and valaciclovir, but

these drugs prevent lesion development, whereas penciclovir does not[6]. However, in our study, it was observed that both acyclovir and penciclovir did not prevent lesion development.

While acyclovir cream is applied at intervals of 4 hours, the instructions of penciclovir cream require application at shorter intervals. Therefore, the use of acyclovir is more practical[15].

Although topical antiviral drugs are generally well tolerated drugs, the most common side effects associated with these drugs are headache and drying of the application area[6]. The patients participating in our study did not report any side effects to the drugs.

The increase in stress level is an important factor in the recurrence of RHL lesions. Schmidt et al. reported that RHL lesions developed following negative experiences and stressful life events[16]. In according to this, it has been reported that cellular immunity weakens and lesions recur as the stress level increases in individuals followed for a long time[17]. Our results showed that 34.2% of the patients with lesions showed moderate or higher symptoms in terms of anxiety and 41.4% in terms of stress. Again, Schmidt et al. reported that the increase in anxiety and stress levels during the recurrence of lesions correlated with lesion development[16]. Similar to our study, it has been reported that an increase in pain sensation can be observed in cases where anxiety increases[18,19]. Although we observed a negative correlation between stress level and pain sensation in our study, it is reported that frequently perceived stress increases the pain[20,21]. In addition, there are studies reporting that there is no significant relationship between pain and stress[22,23].

This study has some limitations. Two different active ingredients were evaluated in our study however, a placebo group was not available. Also, only the topical forms of the drugs were included. This study was designed as an open-label trial therefore, it was liable to bias.

Although it is not possible to cure recurrent herpes labialis completely, any methods and drugs that shorten the healing time of the lesion and reduce pain and discomfort gains importance. Our study showed that acyclovir is superior in reducing pain on third day however, it is not possible to state that acyclovir is the best treatment option for RHL lesions. In order to distinguish the effects of different antiviral drugs more accurately, large-scale randomized clinical trial studies comparing different usage forms and drugs should be investigated for future research.

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