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The Effectiveness of Ganciclovir Comparing with Combination Therapy of Oxytetracycline HCl and Polymyxin B Sulfate in Herpetic Epithelial Keratitis

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Background: Herpes simplex virus is a common keratitis agent. There are two different types of virus, type 1 and 2. Type 1 shows three main clinical pictures in cornea: epithelial herpetic keratitis, stromal keratitis, disciform keratitis. This study aims to reduce the duration of herpetic keratitis treatment and eliminate the risk of complications.

Materials and Methods: Between January 2017 and January 2018, 29 patients with herpetic keratitis were included in the study. In the first group, the herpetic membrane was removed by a single shot on the herpetic lesion with the Yag laser. Then, topically oxytetracycline Hydrochloride+Polymyxin B sulfate was applied. The second group was treated with topical antiviral therapy (Ganciclovir). After treatment, daily follow-up of patients, vision, tonus, fundus diameters and recovery times were noted and the data were compared statistically.

Results: In group-I and group II, the age of the patients did not differ significantly ($p>0.05$). In group-I and group II, the gender distribution of the patients did not differ significantly ($p>0.05$). In Group I and Group II, the degree of vision did not differ significantly ($p>0.05$). In group I and group II, the examination findings were not significant ($p>0.05$). In group I and group II, recovery time was significantly different ($p<0.05$).

Conclusion: Oxytetracycline HCl + Polymyxin B Sulfate may be superior to other interventions for treating herpetic epithelial keratitis.

Keywords: Herpetic epithelial keratitis, ganciclovir, oxytetracycline HCl, polymyxin B sulfate

Introduction

The herpes simplex virus (HSV) is a DNA virus that is a member of the herpesviridae family, and naturally, it can only infect humans. Herpes simplex is an enveloped virus that contains lipid and glycoprotein structures. With this feature, envelopes can be broken with chemical factors. HSV type 1 is seen in the face and eyes, HSV type 2 causes herpetic disease in the genital area. HSV type 1 causes infection 6 months-5 years between the periods of kissing. HSV is transmitted through close contact and saliva and cause primary infection. Primary infection is subclinical with general symptoms of viral diseases in 85-99% of cases. HSV type 1 can form 3 main clinical pathologies in cornea: a) epithelial herpetic keratitis (EHK), b) stromal keratitis, c) disciform keratitis. The incidence of ocular herpes is reported as 5.9 -12% and the majority of these are EHC. Herpes simplex virus-induced keratitis (HSK) is one of the leading causes of corneal blindness in the

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world (1). The primary infection occurs after direct contact of the mucosal membrane with herpes simplex virus-1 (HSV-1). Clinical pictures of the virus occur as a result of the destruction of the cornea (2, 3). The virus then latent in the trigeminal ganglion and leads to recurrent infections (1, 4). There are factors such as age, poor hygiene and socioeconomic class in the etiology (5). Ocular HSV-1 infection is associated with a wide range of ocular pathologies like conjunctivitis, keratitis, irido cyclitis and acute retinal necrosis (6). HSV is a common viral cause of corneal disease (etc. keratitis) and is one of the leading causes of infectious corneal blindness in developed countries (5). Visual loss is most commonly seen in more severe cases with stromal opacification and corneal ulceration (6).

Antiviral agents are the most preferred treatment for HSV epithelial keratitis. Both topical and oral agents are available. Regarding topical agents, both the ganciclovir gel and the trifluridine solution were approved by the FDA (5). Acyclovir and trifluridine ointment have similar efficacy (5) and the same efficacy has been demonstrated when acyclovir ointment compared with ganciclovir (5). Recommended treatment for HSV stromal keratitis includes an oral antiviral agent in combination with a topical corticosteroid agent for at least 10 weeks.

The aim of this study is to reduce the duration of herpetic keratitis treatment and eliminate the risk of complications.

Materials and Methods

Between January 2017 and January 2018, 29 patients with herpetic keratitis were included in the study. The patients were recruited from our hospital. There are 14 patients in the first group, and there are 15 patients in the second group. In group I, herpetic membrane was removed by a single shot on the herpetic lesion with the Yag laser. Then, oxytetracycline hydrochloride+ polymyxin B sulfate was applied topically. The second group was treated with topical antiviral therapy (Ganciclovir). After the treatment, daily follow-up of patients, vision, tonus, fundus diameters and recovery times were noted, and the data were compared statistically.

Statistical Method

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in descriptive statistics of the data. The distribution of the variables was measured with the Kolmogorov Smirnov test. Independent samples t-test, Mann-Whitney U test were used for the analysis of quantitative independent data. Chi-square test was used for the analysis of qualitative independent data. SPSS program was used in the analysis.

Results

Demographic information of the study sample is shown in Table 1. There are 14 patients in the group I, and there are 15 patients in group II. In group-I and II, the age of the patients did not differ significantly ($p>0.05$). In group-I and II, the gender distribution of the patients did not differ significantly ($p>0.05$).

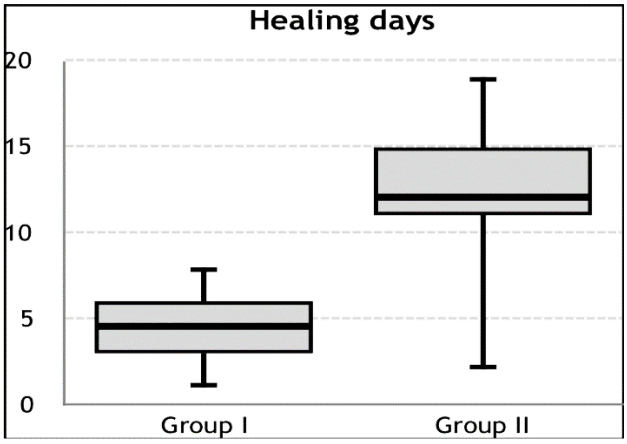

Figure 1. Treatment duration, in the groups.

Group-I and II showed no significant difference in terms of age and gender (p>0.05). In Group I and II, the vision value did not differ significantly (p>0.05). In group I and II, the diagnostic value was not significant (p>0.05). In group I and group II, recovery time was significant (p <0.05) (Table 2)(Figure 1).

Discussion

This study compared combined use of Oxytetracycline HCl and Polymyxin B Sulfate with ganciclovir for the treatment of herpetic epithelial keratitis. This study aimed to reduce the duration of herpetic epithelial keratitis treatment, eliminate the risk of complications like blindness, or infections, minimize the cost of treatment, and increase the satisfaction and quality life of patients.

HSV is known to cause several medical conditions that mostly include central nervous system, eye, mouth, and genitalia. HSV-1 is the most common cause of infectious keratitis around the world, and it usually impairs the quality of life (1, 2). HSV epithelial keratitis can be primary or secondary (recurrent). Primary epithelial keratitis may occur with or without blepharoconjunctivitis. Recurrent keratitis can

Table 1. Demographic variables and examination findings

Variables		Min-Max	Median	Mean ± SD/N%	
Age		27 – 73	47	47.5 ± 14.1	
Gender	Female Male			(15) 51.7% (14) 48.3%	
Eye sides	Right Left			(13) 44.8% (16) 55.2%	
V_o T_o Healing days		1 – 9 11 – 21 2 – 19	4 16 9	4.3 ± 2.2 16.1 ± 2.9 9 ± 4.9	
Fun	Normal			29	100%
Size	n	%	Size	n	%
1x1 mm 1x3 mm 2x1 mm 2x2 mm 2x3 mm 3x1 mm 3x2 mm	1 1 1 3 1 4 5	3.4% 3.4% 3.4% 10.3% 3.4% 13.8% 17.2%	3x3 mm 3x4 mm 4x2 mm 4x3 mm 6x4 mm 6x5 mm	2 1 5 3 1 1	6.9% 3.4% 17.2% 10.3% 3.4% 3.4%

Table 2. The comparison of group I and group II

Variables		Group I			Group II			p
		Mean±SD/N%		Median	Mean±SD/N%		Median	
Age		48.1 ± 13.7		46.5	46.9 ± 14.8		47	0.822
Gender	Male Female	7 7	50% 50%		7 8	46.7% 53.3%		0.858
Eye sides	Right Left	7 7	50% 50%		6 9	40% 60%		0.588
V_o		4.5 ± 2.4		4	4.1 ± 2.1		4	0.756
T_o		16.4 ± 2.4		16.5	15.8 ± 3.3		15	0.599
Healing days		4.6 ± 1.6		4.5	13.1 ± 2.8		12	0.0001

be due to the reactivation of previous epithelial or non-epithelial HSV (3, 4). Primary infection is seen in early childhood. HSV-1 moves into the mucous membrane and epithelial cells by direct contact. The virus goes retrograde through axons to reach trigeminal ganglia, and it develops. On the other hand, the cornea has also been reported to be an area of latency. Although there have been debates on the reactivation of the virus, fever, ultraviolet light, contact lens, surgery, and immunosuppressive therapy have been linked to the reactivation of epithelial keratitis. Reactivation may induce different types of keratitis different from the initial presentation (9).

HSV epithelial keratitis is usually the most painful type of keratitis. It has vesicles and causes itching. Other symptoms include photophobia, blurred vision, redness, burning, foreign body sensation, tearing, and decreased vision. These findings refer the patient to an ophthalmologist. The diagnosis is made by slit-lamp examination. Dendritic and geographic ulcers are two types of HSV epithelial keratitis. They are merely recognizable with the typical pattern after fluorescein staining. This characteristic feature usually eliminates further tests like culture, PCR, immunofluorescence assay (IFA), an immunochromatographic assay, which may be used for the other types of herpetic eye disease (9). Currently, trifluridine (TFT), ganciclovir (GCV), and acyclovir (ACV) are available topical medications, and ACV, valacyclovir (VACV), and famciclovir (FCV) are the most accessible systemic antivirals. Oral ACV, TFT, and topical GCV have been equally effective to treat HSV epithelial keratitis. After being phosphorylated and activated by viral thymidine kinase, all of these medications inhibit viral DNA replication. Based on the disease condition, either topical or systemic antivirals are used for the treatment of HSV epithelial keratitis. Topical antivirals and oral ACV have shown almost similar therapeutic effects for years. A combination of topical and systemic antivirals or even augmenting treatment with epithelial debridement was reported. It is unclear whether these modalities can fortify the treatment (9).

In a study, Komoto et al. (10) compared the effects of ACV ointment, oral VACV, and oral FCV for the treatment of HSV epithelial keratitis on mice. Tear cultures showed that HSV-1 was not detectable in the local ACV group and oral VACV group on day 4, and in the oral FCV group on day 6. The authors declared that a 5-day treatment with these medications would be enough for the treatment. In another study on humans concerning the administration of VACV for the treatment of HSV epithelial keratitis, Sozen et al. (11) showed that VACV was better than topical ACV because faster epithelial healing and lower photophobia were reported in the VACV group. FCV has never been studied for the treatment of HSV epithelial keratitis on humans, but it was sufficient for this purpose in an animal model (12). Compared to these studies, in our study, the duration of herpetic keratitis treatment was very short as four days on humans.

There are different recommendations on the necessity of debridement in ophthalmology books in the treatment of the disease, which is important cause of blindness, such as herpetic keratitis. In some books, it is recommended to start treatment with topical antiviral drugs (bromovinyldeoxyuridine, trifluorothymidine, acyclovir, ganciclovir) in the treatment of EHC. There is a consensus that tropical antiviral agents such as trifluridine, acyclovir and

recently ganciclovir have improved herpetic epithelial keratitis by up to 90% within two weeks.

The current treatment guidelines spread the herpetic keratitis treatment over a long period of 10 weeks (5), but the sociocultural levels of patients were generally low for ten weeks, and the length of the treatment period reduced the rate of treatment use in patients and increased likelihood of recurrence. Therefore, a treatment method and treatment agent are needed for herpetic keratitis to be effective in a shorter time (7, 8).

In our study, the duration of herpetic keratitis treatment was very short as four days, and no significant difference was observed between control vision, tonus, fundus diameter parameters, and topical antiviral treatment. Although this result of the treatment with the same efficacy as the antiviral treatment, we proved this effectiveness in a concise time.

Conflict of Interests

None of the authors has a conflict of interest with the submission.

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