

Comparison of Ganciclovir Gel 0.15 and Acyclovir 3% Ointment for the Treatment of Herpes Simplex Epithelial Keratitis

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Abstract

Background: Eye disease due to Herpes simplex virus (HSV) commonly presents as epithelial keratitis which, though usually self-limiting, may persist or progress without treatment. It is a highly prevalent and visually disabling disease in both pediatric and adult populations.

Aims: To compare efficacy of ganciclovir & acyclovir in the treatment of Herpes simplex epithelial keratitis.

Methods: This randomized controlled trial was carried out in the Department of Community Ophthalmology BSMMU, Dhaka and Ispahani Islamia Eye Institute and Hospital, Dhaka, from October 2019 to February 2021. A total of 38 patients with Herpes simplex keratitis attending outdoor were included in this study. Clinically diagnosed by ophthalmologist, dendritic keratitis or geographic keratitis patients age belonged to 19 - 65 years of both gender were enrolled. The patients were divided into two groups by randomizations to either receiving ganciclovir gel 0.15% considered as group I (n=19) or acyclovir 3.0% ointment considered as group II (n=19) by using the lottery method. The patients were followed up at days 2, 7, 14 and 21.

Results: The mean ulcer size at day 7 were 0.92 ± 0.96 (mm) in group I and 2.28 ± 1.46 (mm) in group II and at day 14 were 0.09 ± 0.41 (mm) in group I and 0.68 ± 0.27 (mm) in group II. The difference was statistically significant ($p < 0.05$) between the two groups.

Conclusion: Ganciclovir 0.15% ophthalmic gel and acyclovir 3% ophthalmic ointment were found equally effective in their ability to heal herpes-induced keratitis in the patients.

Keywords: Herpes simplex virus, Ganciclovir, Acyclovir, Dendritic ulcer, and Geographical ulcer.

Introduction

Eye disease due to Herpes simplex virus (HSV) is the leading cause of ocular morbidity and the number one infectious cause of unilateral corneal blindness in the developed parts of the world.¹⁻⁸ Globally, there are 1.5 million new cases and forty

thousand visual impairment cases report found yearly. Usually, it is a unilateral disease, bilateral involvement is common in younger age groups and immunocompromised patients.⁹

According to the American Academy of Ophthalmology Herpes simplex keratitis (AAO

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HSK) treatment guideline 2014, the treatment approach varies depending on the classification and severity of ocular infection.¹⁰ The AAO HSK treatment Guideline 2014 and Herpetic Eye disease study (HEDS) recommend topical antiviral agents as first-line pharmacotherapy for epithelial HSK.¹¹ More recently developed topical antivirals, such as acyclovir (ACV) and ganciclovir, are more selective and less toxic than their predecessors.^{3, 12}

Several clinical trials have shown ganciclovir 0.15% ophthalmic gel effect on keratitis. The topical formulation is effective, well-tolerated, safe, non-toxic to the ocular surface, and does not cause adverse systemic side effects.^{6-7, 12}

In developing countries like Bangladesh, a significant number of people are suffering from Herpes simplex keratitis. This study has been undertaken to assess the relative efficacy of topical ganciclovir 0.15% gel and acyclovir 3% ointment in the treatment of Herpes simplex epithelial keratitis.

Materials And Method

Randomized control trial was carried out at the Department of Community Ophthalmology, BSMMU and Ispahani Islamia Eye Institute and Hospital, Dhaka from October 2019 to February, 2021. A total of 38 patients with Herpes simplex keratitis attending outdoor were included in this study. Age belonged to 19 - 65 years of both gender, clinically diagnosed by ophthalmologist dendritic keratitis or geographic keratitis patients were enrolled in this study. Patients with keratouveitis, immune deficiency, corneal ulcer, pregnancy, multiple topical drug use and diabetes were excluded. The aim, benefit and procedure of the study were explained to the patient and informed consent was taken from each participant. Ethical clearance was obtained from the Institutional Review Board (IRB) of BSMMU. Complete clinical evaluation including history and relevant ocular examination was done. Patients were divided into two groups. Group I received topical ganciclovir gel 0.15% while Group II received topical 3% acyclovir ointment. Grouping

was based on the random selection of sampling units from the patients by lottery. Either ganciclovir gel 0.15% or acyclovir 3% ointment was applied five times daily and stopped the medication in patients whose ulcer healed within 10-14 days and continued medication in those patients who did not healed up within 21 days.

Base line of examination and administration of treatment were done at day 0, and patients were re-examined on the 2nd, 7th, 14th and 21st days after treatment to assess the rate of healing of HS epithelial keratitis. The size of the ulcer was measured as the greatest length in millimeters with the calipers of the slit lamp bio-microscope.

Statistical analysis was carried out by using statistical package for social sciences version 22.0 for windows (SPSS). Quantitative variables were tested by the student t-test and Chi-Square test was done for quantitative observations

Result

Table I shows the distribution of the study patients by socio demographic parameters. The mean age was 40; 26 ± 11.67 years in group I and 35.79 ± 10.25 years in group II. The mean age difference was statistically not significant ($p > 0.05$) between two groups. In group I and group II, 16 patients (84.2%) and 14 patients (73.7%) were male respectively, the difference in gender was statistically not significant ($p > 0.05$) between the two groups. In this present study, it was observed that patients were involved in different occupations in group I and in group II. The difference was statistically not significant ($p > 0.05$) between the two groups.

Table II shows the distribution of the study patients by affected side. It was observed that more than two third (68.4%) patients affected right eye in group I and 11(57.9%) in group II. The difference was statistically not significant ($p > 0.05$) between two groups.

Table III shows the mean ulcer size at days 0, 2, 7, 14, 21. At day 0, mean ulcer size was 5.71 ± 2.14 (mm) in group I and 3.36 ± 1.36 (mm) in group II. The mean ulcer size at day 2 was 4.13 ± 1.85 (mm)

in group I and 3.05 ± 1.42 (mm) in group II. The difference was statistically significant ($p < 0.05$) between two groups. The mean ulcer size at day 7 was 0.92 ± 0.96 (mm) in group I and 2.28 ± 1.46 (mm) in group II. The difference was statistically significant ($p < 0.05$) between two groups. The mean ulcer size at day 14 was 0.09 ± 0.41 (mm) in group I and 0.68 ± 0.97 (mm) in group II. The difference was statistically significant ($p < 0.05$) between two groups. The mean ulcer size at day 21 was 0.03 ± 0.11 (mm) in group I and 0.32 ± 0.69 (mm) in group II. The difference was statistically not significant ($p > 0.05$) between the two groups.

Figure 1 shows the distribution of the study patients by herpetic epithelial keratitis. It was observed that among the Herpetic epithelial keratitis, dendritic keratitis were in 31 patients (81.6%) and geographic keratitis were found in 7 patients (18.4%).

Figure 2 shows the line chart indicating mean dendritic ulcer sizes (mm) in the two treatment groups.

Table I: Distribution of the study patients by socio demographic parameters (n=38)

Socio demographic parameters	Group I (n=19)		Group II (n=19)		P Value
	N	%	n	%	
Age (in year s)					
19 -29	3	15.8	5	26.3	
30 -39	8	42.2	10	52.6	
40 -49	4	21.0	3	15.8	
50 -59	4	21.0	0	0.0	
>59	0	0.0	1	5.3	
Mean ± SD	40.26±11.67		35.79±10.25		0.336 ^{ns}
Range (min -max)	(20,60)		(20,65)		
Gender					
Male	16	84.2	14	73.7	0.426 ^{ns}
Female	3	15.8	5	26.3	
Occupational Status					
Service holder	2	10.5	3	15.8	0.743 ^{ns}
Business	2	10.5	4	21.1	
Housewife	2	10.5	3	15.8	
Farmer	2	10.5	2	10.5	
Other	11	58.0	7	36.8	

Table II: Distribution of the study patients by affected side (n=38)

Affected side	Group I (n=19)		Group II (n=19)		P Value
	N	%	N	%	
Right eye	13	68.4	11	57.9	0.501 ^{ns}
Left eye	6	31.6	8	42.1	

Table III: Mean dendritic ulcer sizes (mm) in the two treatment groups (n=38)

Size of ulcer	Group 1 (n=19)	Group II (n=19)	P Value
0 days			
Mean ± SD	5.71±2.14	3.36±1.36	0.001 ^s
Range(min -max)	(2,8.5)	(1.4,6.8)	
2 days			
Mean ± SD	4.13±1.85	3.05±1.42	0.051 ^{ns}
Range(min -max)	(0,6.5)	(0.5,6.2)	
7 days			
Mean ± SD	0.92±0.96	2.28± 1.46	0.001 ^s
Range(min -max)	(0,3 -2)	(0,5)	
14 days			
Mean ± SD	0.09±0.41	0.68±0.97	0.019 ^s
Range(min -max)	(0,1.8)	(0,3)	
21 days			
Mean ± SD	0.03±0.11	0.32±0.69	0.078 ^{ns}
Range(min -max)	(0,0.5)	(0,2)	

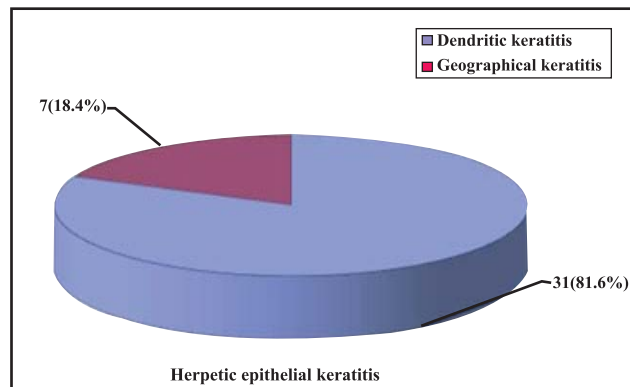


Figure 1: Pie chart showing distribution of the study patients by herpetic epithelial keratitis

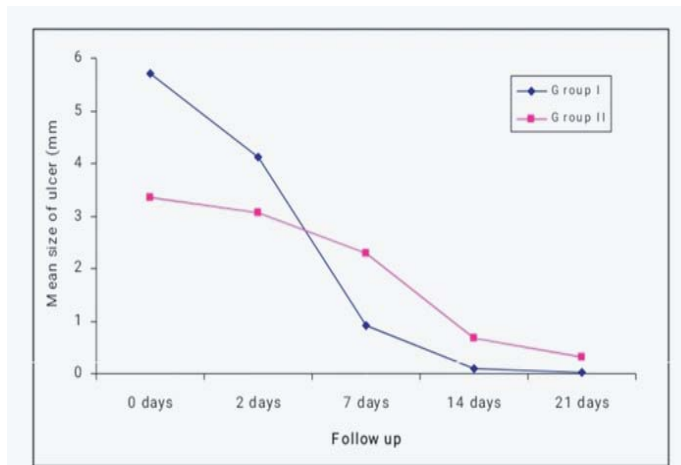


Figure 2: Line chart showing mean dendritic ulcer sizes (mm) in the two treatment groups.

Discussion

In this current study, the mean age was 40.26 ± 11.67 years in group I and 35.79 ± 10.25 years in group II. The mean age difference was statistically not significant ($p > 0.05$) between the two groups. Hoh et al. (1996) observed in their study that the mean age was 43.5 years varying from 24 to 68 years in the ganciclovir group while in the acyclovir treatment group, mean age was 53 years varying from 33 to 83 years, which is higher in comparison to the present study.¹³ The higher mean age and age range obtained by the above author may be due to geographical variations, racial, ethnic differences, and genetic causes that may have a significant influence on their study subject.

In this present study, it was observed that Herpes simplex epithelial keratitis was more common in male subjects, where 84.2% and 73.7% of patients were male in group I and group II respectively. The difference was statistically not significant ($p > 0.05$) between the two groups. The male to female ratio was 5.3:1 in group I and 2.8:1 in group II. Chauhan et al. (2019) in their study reported that viral corneal ulcer was found to be more common in males as compared to females, which was 63.2% in males and 34.6% in females¹⁴, which is consistent with the current study.

The mean ulcer size declined in all subsequent follow-up from day 0. The mean ulcer size at day 2 were 4.13 ± 1.85 (mm) in group I and 3.05 ± 1.42 (mm) in group II; at day 7, 0.92 ± 0.96 (mm) in group I and 2.28 ± 1.46 (mm) in group II; at day 14 it were 0.09 ± 0.41 (mm) in group I and 0.68 ± 0.97 (mm) in group II; and at day 21 ulcer size were 0.03 ± 0.11 (mm) in group I and 0.32 ± 0.69 (mm) in group II. The mean ulcer size was statistically significant ($p > 0.05$) on days 7 and 14 between the two groups but not significant ($p > 0.05$) on days 2 and 21 between the two groups. However, the ulcer was healing early in group I. In group I, one patient had late healing, and two patients healed after 21 days in group II. One patient lost follow-up in group I and three patients lost follow-up in group II.

Chauhan et al. (2019) found that the ulcer size was not significantly different on days 1, 7, and 14 in ganciclovir and acyclovir groups. The ulcers completely healed by day 21 in both groups. There was no significant difference in the ulcer size on the follow-up visits in the two groups. By the 14th day, 80.0% of ulcers were healed in Group I while 88.0% healed in Group II. There was no significant difference in the time required for healing in the two groups¹⁴.

Several clinical trials had shown ganciclovir 0.15% ophthalmic gel to be both safe and effective; the topical formulation is well-tolerated, nontoxic to the ocular surface, and does not cause adverse systemic side effects.^{3, 7-8, 13, 15} In the largest trial showed median time to recovery was similar for the 2 treatments, generally ranging from 6 to 7 days with ganciclovir (9 days in the geographic ulcer stratified group) versus 7 to 8 days with acyclovir ointment.¹⁶ A post hoc analysis of the larger trial concluded that ganciclovir gel was non inferior to acyclovir ointment.⁴

The treatment cost for ganciclovir gel 0.15% is 200.00 Taka and acyclovir 3% cost varied from 40 to 100 Taka in our country.

Conclusion

This study was undertaken to compare the efficacy of the ganciclovir and acyclovir in the treatment of epithelial keratitis. Dendritic keratitis was more common than Geographic keratitis and the peak age group was 4th decade. Herpes simplex epithelial keratitis was more common in male subjects. This study showed that ganciclovir 0.15% ophthalmic gel is an equally effective and safe alternative to acyclovir 3% ophthalmic ointment in the treatment of herpes simplex dendritic ulcers with the advantage of having less effect on the blurring of vision owing to its water miscible property. So, the safety profile of both the drugs (acyclovir and ganciclovir) was found to be similar. Acyclovir is cost-effective in our country.

Limitation

1. The present study to assess two varieties of epithelial keratitis. All the spectrum of viral keratitis is not included here.

2. This study found more dendritic keratitis than geographical ulcer.

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