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Original Research Article

Efficiency of ganciclovir ophthalmic gel of 0.15% in treatment of acute adenoviral keratconojunctivities

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ABSTRACT

Background: Adenoviral eye infection is contagious, self-limiting, causing symptoms like burning, pain, photophobia, and tearing. Diagnosis is clinical; existing treatments lack consistency. Ganciclovir, a selective and less toxic antiviral, shows promise for inhibiting viral DNA synthesis. The primary objective of this study was to assess the efficacy of topical 0.15% Ganciclovir gel in treating adenoviral keratoconjunctivitis, focusing on symptom and sign improvement during the follow-up period.
Methods: A study at the National Institute of Ophthalmology and Hospital included 40 adenoviral keratoconjunctivitis patients diagnosed by cornea specialists. Symptoms were scored on a 0-3 scale during a 6-week follow-up. Patients were randomly assigned to group 1 (0.15% ganciclovir) or group 2 (artificial tear control). Data included history and ophthalmic exams. Statistical analyses used SPSS version 13.0 with $p<0.05$ significance, employing unpaired t-tests and chi-square tests.
Results: A study with 40 adenoviral keratoconjunctivitis patients assessed Ganciclovir 0.15% ophthalmic gel efficacy. No age difference between groups was observed. Most patients were male (82.5%), spanning different economic classes. Symptom variations included more foreign body sensation in group 1 and increased watering in group 2. Group 1 exhibited faster symptom improvement over 6 weeks, while group 2 had a slower decline. Both groups experienced complications, but group 1 showed faster recovery, suggesting Ganciclovir's potential efficacy in treating adenoviral keratoconjunctivitis.
Conclusions: In summary, the study confirms the effectiveness of 0.15% Ganciclovir gel in treating acute adenoviral keratoconjunctivitis, showing statistically significant and rapid improvement in signs and symptoms.

Keywords: Adenoviral eye infection, Ganciclovir, Keratoconjunctivitis

INTRODUCTION

Adenoviral eye infection is a self-limiting, highly contagious and very frequent infectious process that can occur in epidemic outbreaks.[1,2] It can present in three acute clinical forms: nonspecific acute follicular conjunctivitis, pharyngo-conjunctival fever and epidemic keratoconjunctivitis.[3,4] The patient has complaints of burning, pain, photophobia, pruritus, irritation and tearing.[1,2] It may range from mild inflammation with

diffuse conjunctival hyperemia and follicular and papillary reaction to severe inflammation with subconjunctival hemorrhage, pseudo-membranes or tarsal membranes.[1-3] Onset is acute, with symptoms 6 to 9 days after exposure. The ocular picture is usually bilateral, occurring simultaneously or with a difference of three days between the two eyes and in general, the second picture is lighter.[3,4]

The diagnosis of adenoviral conjunctivitis is generally clinical, based on signs and symptoms, and epidemiological. Laboratory diagnosis of adenoviral infections is rarely indicated and currently is based on cell-culture in combination with immunofluorescence staining (CC-IFA), serologic methods, antigen detection, or PCR.[5] Cell culture in combination with immunofluorescence staining (CC-IFA) is the historical gold standard but is not widely used. Since its introduction as a laboratory test for eye disease in 1990 PCR has been used widely in clinical ophthalmology and has demonstrated better sensitivity compared with cell culture.[6,7] Several drugs have been tested for the treatment of viral conjunctivitis, such as cyclosporine, trifluridine, povidone iodine, cidofovir, but none of them proved to be effective.[8]

There is no specific or prophylactic treatment to prevent inter-human contagion or transmission to the patient's second eye. Some agents such as ganciclovir have shown potential benefits for this condition and for this reason this study was conducted. Topical ganciclovir is already marketed in several countries in Europe, Asia, Africa and South America for treatment of ocular herpes. Ganciclovir is a more selective and less toxic antiviral compared to other older antivirals.[9] Ganciclovir and aciclovir have similar pharmacological mechanisms: thymidines kinases convert ganciclovir into an active triphosphate derivative, mainly in infected cells. Once phosphorylated, ganciclovir inhibits viral DNA synthesis in two ways: competitive inhibition of viral DNA polymerase and direct incorporation inside the viral DNA primer, which results in the termination of viral DNA chain and prevents viral replication.[9]

Topical application of gancilovir has been shown to penetrate the corneal stroma and reach the aqueous humor at therapeutic levels.[10] Ganciclovir, a synthetic deoxyguanosine-2, nucleoside analog showed be a potent inhibitor of viral replication not only for adenovirus but also HSV1, HSV2, HZV, EBV, CMV, HHV6, hepatitis B virus.[11-13] Ganciclovir has been shown to be a safe and effective topical antiviral, with less toxicity and more convenient dosage.[9,10,14] There are few clinical trials regarding the use of ganciclovir in adenoviral keratoconjunctivitis. Study suggested that ganciclovir can help to achieve faster resolution of sign and symptoms reduce the contagiousness of the disease and prevent subepithelial opacities Although there are many studies to find an effective drug in the treatment of adenoviral ketaroconjuctivitis none have been conclusive.[14,15] Due to the need for effective treatment for this common and highly contagious condition, the present clinical trial was conducted.

This study aimed to assess the efficacy of topical 0.15% ganciclovir gel in the treatment of acute adenoviral keratoconjunctivitis. Also, to assess the clinical improvement after treatment with topical 0.15% ganciclovir gel, to assess signs of the study subjects during follow up period after starting treatment with topical 0.15% ganciclovir gel.to compare mean score of symptoms before and after the treatment, to compare mean score of signs before and after the treatment, to assess improvement and recovery time, to compare the complications between two groups.

METHODS

This Quasi-experimental study was conducted in the Department of Cornea, National Institute of Ophthalmology and Hospital, Dhaka since June 2020 to July 2021, comprising 40 cases of adenoviral keratoconjunctivitis who attended the cornea clinic, selecting them by non-random purposive sampling technique.

Inclusion criteria

Patient with acute viral keratoconjunctivitis with onset of symptoms 5 days or less, be over 18 years old were included in the study.

Exclusion criteria

Patients with central or para central corneal opacities, pregnant or nursing women and patient with other immunodeficiency, patients with corneal dystrophy, degeneration and corneal ecstatic condition, patients with previous ocular surgery (previous keratoplasty), patients with kerato-uveitis, patient with corticosteroid or antibiotic use by any route within 30 days prior to the study, one eyed patients were excluded.

This 40 patients of viral keratoconjunctivitis with symptoms onset 5 days or less non randomly divided into two groups: group-i (treatment group) with 20 patients who used 0.15%ganciclovir and group-ii (control group) with 20 patients who used artificial tear and 0.5% moxifloxacineye drop for 6 weeks. Data was collected from both group. All patients with viral keratoconjunctivitis had gone ophthalmic examination. A data sheet was filled by interviewer by face to face interview.

They were followed-up by same examiner by same questionnaire on 1week, 2 weeks, 4 weeks and 6 weeks. Mean score of symptoms and signs were calculated in every follow-up and compared between two groups.

Statistical analyses were done to assess the level of significance. All the relevant data was recorded in a pre-designed data collection sheet. The Statistical analysis was performed using the SPSS program, version 13.0.Unpaired t test and Chi square test were done in applicable cases. At 95% CI, p-value <0.05 will be considered as significant.

RESULTS

This study was conducted over 40 patients of adenoviral keratoconjunctivitis to assess the efficacy of ganciclovir 0.15% ophthalmic gel in the treatment of adenoviral keratoconjunctivitis. Results are presented with appropriate tables.

Table 1 show the age distribution of the study subjects. In group 1, out of 20 patients 15-25 years was 0, 25-35 was 8, 35-45 was 8, 45-55 was 3, 55-65 was 1, mean age was 36.4±9.59 (SD) years. In group 2, out of 20 patients 25 years was 3, 25-35 was 3, 35-45 was 10, 45-55 was 3, 55-65 was 1, mean age was 37±11.02 (SD) years. Difference between two groups was statistically non-significant.

Table 1: Age distribution of the study subjects.

Age group	Group-1	Group-2	P
15-25 years	0	3	
25-35 years	8	3	
35-45 years	8	10	
45-55 years	3	3	
55 years or more	1	1	1.0^{ns}
Total	20	20	
Mean age	36.4±9.59 (SD)	37±11.02 (SD)	

Table 2 shows gender distribution of the study subjects. Among 40 patients 33 were male and 7 were female. In group 1 out of 20 patients 17 were male and 3 were female. In group 2 out of 20 patients 16 were male and 4 were female. Sex distribution in the study groups out of 40 patients 82.5% were male and 17.5% were female. Regarding distribution of economic status, patients were categorized into upper, middle and lower class according to monthly income of themselves or their parents. Those who have monthly income less than Tk.10,000/- were categorized into lower class, Tk.10,000/- to 40,000/- were categorized into middle class and Tk.40,000/- or more categorized into high class. Among 20 patients in group 1, 2 patients belongs to lower class, 15 patients belongs to middle class and 3 patients belongs to upper class. In 20 patients of group 2, 2 patients belongs to lower class, 16 patients belongs to middle class and 2 patients belongs to upper class. In occupational status in both study groups. In group 1, 12 patients were service holder,3 were day labor, 2 were student, 2 were house maid and 1 was housewife. In group 2, 14 patients were service holder, 2 were day labor, 2 were student, 1 was house maid and 1 was housewife.

Table 2: Gender distribution of the study subjects.

	Group-1	Group-2	P
Gender			
Male	17	16	
Female	03	04	1.26^{ns}
Total	20	20	
Economic status			
Lower class	02	02	2.08
Middle class	15	16	
Upper class	03	02	
Occupational status			
Service holder	12	14	
Day labor	3	2	
Student	2	2	2.13ns
House maid	2	1	
House wife	1	1	

Table 3 shows the distribution of frequency of symptoms at presentation in both study groups. In group 1, 19 patients presented with FB sensation, 18 with photophobia, 18 with watering, 10 with discharge, 12 with eye ache, 6 with reduced vision. In group 2, 20 patients presented with watering, 18 with photophobia, 17 with FB sensation, 9 with discharge, 18 with eye ache and 4 with reduced vision.

Table 3: Distribution of frequency of symptoms at presentation of the study subjects.

Symptoms	Group-1	Group-2	P
FB sensation	19	17	
Watering	18	20	
Photophobia	18	18	1^{ns}
Discharge	10	9	
Eye ache	12	18	
Reduced vision	6	4	

Table 4: Distribution of frequency of signs at presentation of the study subjects.

Symptoms	Group-1	Group-2	P
Intact corneal sensation	20	20	
Punctate epithelial keratitis	20	20	0.16^{ns}
Reduced visual acuity	18	20	
Conjunctival congestion	18	16	

Table 4 shows distribution of frequency of signs at presentation in both study groups. In group 1, 20 patients presented with intact corneal lesion, 20 patients with punctate epithelial keratitis, 18 patients with reduced vision acuity and18 with conjunctival congestion. In group-2, 20 patients presented with Intact corneal lesion, 20 patients with punctate epithelial keratitis, 20 patients with reduced vision acuity and 16 with conjunctival congestion.

Table 5 show that the mean score of symptoms during follow up periods after starting treatment with ganciclovir. In group 1, mean score of symptoms at the beginning of the study was 1.4±0.45 (SD), it was 1.14±0.49 (SD), 0.64±0.29 (SD), 0.20±0.25 (SD) and 0.04±0.14 (SD) after 1 week, 2 weeks, 4 weeks and 6 weeks respectively after starting treatment. In group 2, mean score of symptoms at the begging of the study was 1.48±0.26 (SD), it was 1.46±0.28 (SD), 1.13± 0.25(SD), 0.59±0.18(SD)and 0.23 ±0.21(SD) after 1 weeks, two weeks, 4 weeks and 6 weeks respectively after starting treatment.

Table 5: Distribution of mean score of symptoms during different assessment periods.

Assessment periods	Group-1	Group-2	P
Baseline	1.4±0.45 (SD)	1.48±0.26(SD)	0.6^{ns}
1 week after treatment	1.14±0.49(SD)	1.46±0.28(SD)	0.02^{s}
2 weeks after treatment	0.64±0.29(SD)	1.13±0.25(SD)	0.0001^{s}
4 weeks after treatment	0.20±0.25(SD)	0.59±0.18(SD)	0.0001^{s}
6 weeks after treatment	0.04±0.14(SD)	0.23±0.21(SD)	0.0016^{s}

Table 6 shows the distribution of complications of the study subjects at the end of the study. In group-1, 7 patients had pseudomembrane and 5 patients had sub-epithelial infiltrate. In group-2, 5 patients had pseudomembrane and 9 patients had sub-epithelial infiltrate.

Table 6: Distribution of complications of the study subjects at the end of the study.

Complications	Group-1	Group-2	P
Pseudo-membrane	7	11	1.12^{ns}
Sub-epithelial infiltrate	5	9	

Table 7 shows the distribution of days of improvement and recovery after treatment. In group-1, patients improved after 8.40±2.6 (SD) days and recovered after 34.20±8.3 (SD) days. In group-2, patients improved after 18.70±3.6 (SD) days and recovered after 42.85±6.14 (SD) days.

Table 7: Distribution of days of improvement and recovery after treatment.

	Group-1	Group-2	P
Improved	8.40±2.6 (SD)	18.70±3.6 (SD)	$<0.001^{s}$
Recovered	34.20±8.3 (SD)	42.85±6.14 (SD)	$<0.001^{s}$

DISCUSSION

Adenoviral keratoconjuctivitis is a common ocular problem prevailing in our society. Transmission occurs more readily in populations living in close quarters, such as schools, nursing homes, military housing and summer camps. In this study, patients were within 18-60 years of age. This age range was chosen as most people within this range work outside and in crowd so chance of adenoviral infection more. Again bellow 18 years is pediatric age group so it was avoided Group 1 comprised 20 patients with age distribution as follows: 25-35 years (8), 35-45 years (8), 45-55 years (3), 55-65 years (1); mean age was 36.4+/-9.59 (SD). Group 2 also had 20 patients with age distribution: 25-35 years (3), 35-45 years (10), 45-55 years (3); mean age was 37+/-11.02 (SD). The difference in age between the two groups was not statistically significant. In both groups, 82.5% were male and 17.5% were female. The majority (95%) presented with watering, followed by reduced vision (50%), discharge (47.5%), eye ache (75%), FB sensation (90%), and photophobia (90%).

Males, being more engaged in outdoor activities, were predominantly affected. A study showed that patients with adenoviral keratoconjunctivitis presented with tearing, photophobia, FB sensation and discharge which is consistent with this study findings. In this study corneal lesion was found in all the patients (100%) on examination at the beginning of the study, this was followed by congestion (85%) and reduced visual acuity (95%).[14] All the patients presented at the beginning of the study with intact corneal sensation in both study group and control group. A study shows that the patients of severe adenoviral keratitis had congestion, hyperemia, corneal lesion and sub epithelial infiltration, which is consistent with this study findings.[15] They did not find reduced corneal sensation in adenoviral keratoconjunctivitis patients which also co relates with this study. By comparing proportion of subsidation of signs of both groups it appears that topical gancyclovir 0.15% eye gel is more effective in relieving signs of corneal lesion, congestion and reduced visual acuity as compared to artificial tear after 6 weeks of treatment.

A study showed that topical gancyclovir 0.15% eye gel is more effective in relieving symptoms and signs of tearing, congestion, corneal lesion, sub epithelial opacities as compared to placebo (preservative free artificial tear) after 2 weeks of treatment.[15] Our study result correlates with this study findings. In this study, the mean score of symptoms during follow up periods after

starting treatment with gangyclovir eye gel in study group and artificial tear in control group shows that in study group, mean score of symptoms at the beginning of the study was 1.4. It was 1.14, 0.64, 0.20 and .04 after 1 week, 2 weeks, 4 weeks and 6 weeks respectively after starting treatment and in control group, mean score of symptoms at the beginning of the study was 1.48, it was 1.46, 1.125, 0.59 and 0.23 after 1 week, 2 weeks, 4 weeks and 6 weeks respectively after starting treatment. A study shows that there is faster improvement of symptoms in study group compared to control group which supports my study findings.[15]

The most frequent manifestation of ocular adenoviral infection is epidemic keratoconjunctivitis (EKC). The distinguishing feature of presentation of EKC is the involvement of the entire ocular surface, including both the conjunctival and corneal epithelia. In severe cases, there may be formation of pseudomembranous and symblepharon as well as multifocal subepithelial infiltrates that can reduce vision for years.[16,17] According to data from Germany, the infection is more common in adults, though all age groups may be affected. There is no sex predilection.[18] In general, EKC typically occurs in the 20 to 40 year age.[19] These focal lesions may represent a cellular immune reaction against viral antigens deposited in the corneal stroma under the Bowman membrane.[20] The complications of the study subjects at the end of the study, in group-1, 7 patients had pseudomembrane and 5 patients had sub-epithelial infiltrate. In group-2, 5 patients had pseudomembrane and 9 patients had sub-epithelial infiltrate.

In our study, there was corneal sub epithelial infiltrates, conjuctival pseudo membranes were higher in group 2 compared to group 1. So, study showed fewer complications in the ganciclovir group. Study shows the distribution of days of improvement and recovery after treatment in group-1, patients improved after 8.40±2.6 (SD) days and recovered after 34.20±8.3 (SD) days. In group-2, patients improved after 18.70±3.6 (SD) days and recovered after 42.85±6.14 (SD) days. So, faster recovery was shown in group 1 ($p<0.001$). Viral cell cultures of the conjunctival specimen allow confirmation of the adenovirus with immunofluorescence, but are less commonly performed because of the necessity for elaborate equipment, trained laboratory personnel, and the significant delay in obtaining results.[21,22] A study found that ganciclovir significantly reduced both the duration of disease and the incidence of subepithelial infiltrates. They found mean time of adenovirus recovery was significantly shorter for ganciclovir-treated patients at 7.7 days in contrast to 18.5 days for those who received artificial tears ($P < 0.05$).[14]

The study has several limitations that warrant consideration. Firstly, the short duration of follow-up poses challenges in capturing the long-term outcomes of the interventions under investigation. Additionally, the relatively small sample size may limit the generalizability of the findings to broader populations. Long-term results were not assessed, preventing a comprehensive understanding of the sustained effects of the interventions. Moreover, the diagnosis was solely confirmed on a clinical basis, lacking confirmation through microbiological and immunological investigations, potentially affecting the accuracy of the results.

CONCLUSION

The present study showed a tendency for faster improvement of signs and symptoms of patients treated with 0.15% galciclovir gel compared to the control group which was statistically significant. The high rate of symptomatic improvement and clinical response demonstrates that this therapeutic modality is an effective method for treatment of acute adenoviral keratoconjuctivitis.

Recommendations

Further studies should be done maintaining the all the criteria of randomized clinical trial to assess the efficacy of topical gancyclovir 0.15% gel in controlling adenoviral keratoconjunctivitis.

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