THE EFFECTS OF ORAL ACYCLOVIR IN THE TREATMENT OF NECROTIZING HERPETIC KERATOUVEITIS

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Abstract - This study was conducted to evaluate the effects of administering oral acyclovir in conjunction with topical acyclovir and steroids in the treatment of necrotizing herpetic keratouveitis. All patients with necrotizing herpetic keratouveits who have been consulted during 1996-1997 at the Farabi Eye Hospital were studied. The patients were randomly assigned to two groups. In the first group, topical acyclovir ointment and topical steroids were administered, while the second group took oral acyclovir, 1600 mg in four divided doses in addition to the above mentioned treatment. The patients undervent follow-up examination every three days in the first three weeks and thereafter periodically for one year.

After three weeks, 92% and 88% improvement was observed in the first and second groups, respectively. The observed difference was not statistically significant. Making nonpharmacologic interventions such as application of soft contact lenses, corneal grafts, and conjunctival flaps were inevitable in some cases in both groups. Secondary infection was observed in three patients (first group) and two patients (2nd group).

The sample size was not large enough to draw a definite statistical conclusion, but it seems that the addition of oral acyclovir has no added effect in the treatment of necrotizing herpetic keratouveitis than topical acyclovir and steroids. In this study, the males were affected more frequently than females.

Acta Medica Iranica 38 (1): 43-49; 2000

Key Words: Herpes simplex virus, keratitis, acyclovir

INTRODUCTION

Herpes simplex is the most common cause of human viral infections (1) and is considered the most common cause of corneal blindness in Western countries (2). Except in an advanced stage, the infection shows a good response to drug therapy. End-stage infection manifests as necrotizing herpetic keratouveitis (NHKU). The pathogenesis of this condition is complex and consists ot direct viral invasion and host immune reactions; therefore a protracted and unpredictable course is witnessed (1,2,3,4,7,8,9). At this stage some of the complications such as corneal opacity, vascularization, and corneal perforation can be minimized by administering appropriate therapeutic regimens. Numerous studies have been conducted and are presently under way in different countries of the world. Older drugs such as iodoxyuridine (IDU) and trifluoridine (F3T) have little effect on KHMU, because the penetration of these drugs to deep corneal stroma and anterior chamber is not sufficient. Therefore, administration of acyclovir was considered in this regard. FDA has approved only the oral form of acyclovir for this purpose (1,2,3,4). Schwab in 1988 (12), Collin in 1993 (29), and Cheng in 1995 (20) demonstrated that acyclovir tablet, with a dose of 200mg, five times per day for 2-3 weeks was effective in different forms of herpetic keratitis. Schwab (12) believes that the improvement observed in NHKU is due to topical steroid therapy and the consequent suppression of immunologic reactions which results in decreased inflammation and improved epithelial repair.

Sanitato (15), while confirming the presence of viral particles in the corneal stroma of his patients, has not reported any beneficial effect for oral and topical acyclovir without steroid therapy. One of the studies in this regard has been Herpetic Eye Disease Study (HEDS). This has been conducted in three separate phases. According to the results of the first phase (7), steroid therapy can be effective in the treatment of herpetic stromal keratitis. In the second phase of the study (8), combination of oral acyclovir with topical steroid therapy and F3T drop has been reproted to be associated with little success (approximately 25%) in control and acyclovir groups. The third phase of the study (9) claims oral acyclovir to be effective in herpetic iridocyclitis. In a paper, titled "Herpetic Eye Disease Study: you can help", the researchers have encouraged the specialists of all countries to present their respective study results, since they did not consider their own results to be sufficient and conclusive.

Therefore no global consensus has yet been achieved in this regard. Additionally there has been no such research in Iran. In view of the serious risks of necrotizing herpetic keratouveitis in jeopardizing the patients' eyesight, this study was conducted to assess the therapeutic effects of oral acyclovir in combination with

topical acyclovir in the treatment of the acute stage of this disease. The study population were patients referred to Farabi Eye Hospital during a one-year period (1996-1997). The hypothesis of better and quicker efficiency of oral acyclovir tablets was therefore tested.

MATERIALS AND METHODS

This study is a clinical trial in 50 patients referred to Farabi Eye Hospital, Tehran during one year. The diagnosis of the disease was based on clinical assessment and positive history of ophthalmic herpes infection. The relevant factors in the history of patients were prior ophthalmic herpes infection, continued problems following chronic or relapsing epithelial herpetic keratitis, any relapsing corneal disease, and unilaterality of the lesion. The following clinical findings have been used in the diagnosis and definition of this stage of the disease: corneal ulcer manifesting as yellow-white caseous necrosis, stromal infiltration or abscess, corneal melting, thinning of the involved corneal stroma, stromal edema surrounding the ulcer, corneal epithelial defect, corneal vascularization, anterior chamber reaction such as presence of cells, flare, and occasionally hypopyon and hyphema, loss of corneal sensation with or without increased intraocular pressure (Fig. 1).

According to this definition, among the referred patients, fifty cases were selected. Those with inconclusive or suspicious findings, secondary infection, or multiple, incomplete courses of treatment were excluded from the study. Additionally, the patients who did not have regular visits during the first three weeks of the study were also excluded. The selected patients were randomly assigned to two groups.

Group A: In this group, therapy consisted of acyclovir ophthalmic ointment 3% (Wellcome, U.K) five times daily; dexamethasone opthalmic drop 1% (Daroupakhsh, Iran) two times daily in the first two days, and subsequently four times daily; homatropine drop 2% (Daroupakhsh, Iran) two times daily; and acetazolamide tablet, 250 mg (Razi, Iran) in the case of increased intraocular pressure with the dosage of 250 mg every six hours for those weighing more than 40 kg, and 125 mg every six hours for those weighing less than 40 kg.

Group B : In addition to the medications administered to the first group, acyclovir tablet, 200 mg (Roozdarou, Iran) was prescribed to these patients with a dosage of two tablets every six hours (1600 mg daily) for those weighing more than 40 kg, and one tablet every six hours (800 mg daily) for those weighing less than 40 kg.

The course of therapy was continued for a period of three weeks in both groups. Prior to including each patient in the study, different aspects of treatment were explained to him/her and an informed consent was thus obtained. The results of therapy in both groups were recorded regularly. The patients were advised against abruptly discontinuing their medication and were asked to rapidly consult their physician in case of exacerbation of symptoms.

Therapeutic soft contact lens was used in some patients and chloramphenicol eye drops were prescribed two times daily to prevent superimposed infection. A questionnaire, containing the following items was filled out for each patient : age, sex, history of ophthalmic herpes, past and present drug history, chief complaint, date of referral, date of the first symptoms of the disease, the assigned treatment group, and personal identification number.

By performing physical examination, the afflicted eye was determined, the aided visual acuity measured and the presence of preauricular adenopathy checked. Thereafter the following factors were studied by a Haag-Streit slit lamp: conjunctival hyperemia, surface area of the lesion in square millimeters, location of the lesion, thickness of the lesion, presence of necrosis, condition of iris, the presence of anterior chamber reaction, the condition of the lens, perilesional infiltration and edema, thinning of the center of the lesion, and measurement of intraocular pressure (if direct measurement was impossible, a rough estimate was used by manual examination). Corneal sensation was measured by Bonnet - Cochet esthesiometer and the results were recorded for all quadrants. The visual acuity was measured by a Snellen chart.

The patients were examined regularly according to the following schedule: every other two days duting the first two weeks; Every week until the end of the first month; every other week during the second month; every month until the end of the sixth month; and every other month during the second six-month period.

The results of the first three weeks of therapy were studied in this research. The indices of successful treatment on examination were: improvement in best aided visual acuity, improvement in corneal sensation, alternation in anterior chamber reaction, ablteration in surface area and thickness of corneal lesion (the degree of infiltration, necrosis, and edema).

Refractoriness to treatment and nonpharmacologic interventions (including therapeutic soft contact lens, corneal graft with conjunctival flap, or scleral graft) were recorded. Secondary infection was studied by bacterial and fungal cultures. The results were examined by Fisher, Chi-square, and McNemar statistical tests.

RESULTS

The age of the patients was 55.4 ± 25 and 51 ± 22 years in the two study groups A and B, respectively. The observed age difference was not statistically significant. Other personal characteristics and clinical findings were also studied and the results are reflected in table 1. The difference in the clinical findings of the two groups was not significant (P> 0.05).

The results of ophthalmologic examination of the patients with necrotizing herpetic keratouveitis are stated in table 2. As observed clearly, the ophthalmologic findings in the study and control groups are either identical or minimally different, lacking statistical significance. Therefore it is concluded that the two groups are identical in this regard.

Table 1. Personal and clinical characteristics in the two groups of patients with necrotizing herpetic keratouveitis, at Farabi Eye Hospital during 1996-97.

	Conrols (Group A)	Cases (Group B)
Age	55.4 ± 25	51.5 ± 22
Sex		
male	20	19
female	5	6
History of ophthalmic herpes	20	3
One - eyed patients	4	2
History of previous eye surgery	2	2
Preauricular adenopathy	3	2
Associated conditions:		
Dry eye	10	12
Trachoma	8	10
Blepharitis	11	10
Trichiasis & entropion	5	6
Exophthalmos	1	0

The changes in ophthalmologic examination findings in the two groups during the course of treatment were studied and are presented in table 3. Chi-square analysis did not show a statistically significant difference.

Secondary infection during treatment was observed in three cases of group A (12%) and two cases of group B (8%). The observed difference is not statistically significant. In these cases, culture study revealed fungal infection in one case, bacterial infection in two cases in group A and bacterial infection in two cases in group B. Administering nonpharmacologic therapy was essential during the active phase of the disease. Six patients in group A and nine in group B received nonpharmacologic therapy, including soft contact lenses in fifty percent of the cases. After the active phase of the disease, six patients in group A and eight patients in group B required nonpharmacologic measures. Soft contact lens was utilized in sixty percent of these cases. The recurrence rate after the active phase of the disease (beyond three weeks) was observed to be 8 percent (two cases) in group A and twenty percent (five cases) in group B. Fisher's exact test revealed this difference to group be statistially insignificant.

Table 2. Ophthalmologic examination findings in patients with necrotizing herpetic keratouveitis before initiating treatment with topical acyclovir (controls) and topical and oral acyclovir (cases) at Farabi Eye Hospital during 1996-97

Ophthalmic examination	Controls N=25	Cases N = 25
Positive anterior chamber reaction	24	25
Corneal changes such as thickness, infiltration, necrosis	25	25
Infiltration & necrosis surface area more than 5 mm^2	23	23
Haziness of iris pattern due to corneal and anterior chamber changes	20	19
Corneal edema exceeding 20% of corneal thickness	25	25
Disturbance in corneal sensation	25	25
Visual acuity : less than FC 1 m	20	19
more than FC 1 m	5	6
Increased intraocular pressure	18	17
Cataract	12	13
Posterior synechia	8	10

Table 3. Distribution of ophthalmologic findings in patients with necrotizing herpetic keratouveitis before and after treatment with topical acyclovir (group A) and topical and oral acyclovir (group B) at Farabi Eye Hospital during 1996-97

Clinical Examination	Group A (%)		Group B (%)	
	Before treatment	After treatment	Before treatment	After treatment
Positive anterior chamber reaction	24 (96)	2 (8)	25 (100)	2 (8)
Infiltration and necrosis	25 (100)	3 (12)	25 (100)	4 (16)
Infiltration and necrosis area more than 5 mm^2	23 (92)	2 (8)	23 (92)	5 (20)
Dense lesion with haziness of iris pattern	20 (8)	3 (12)	19 (76)	3 (12)
Edema exceeding 20% of corneal thickness	25 (100)	3 (12)	25 (100)	5 (25)
Disturbance in corneal sensation	25 (100)	9 (36)	25 (100)	12 (48)
Visual acuity : Less than FC 1 m	20 (80)	6 (24)	19 (76)	6 (24)
More than FC 1 m	5 (20)	19 (76)	6 (24)	19 (76)
Cataract	12 (48)	13 (52)	13 (52)	13 (52)
Posterior synechia	8 (32)	5 (20)	10 (40)	6 (24)

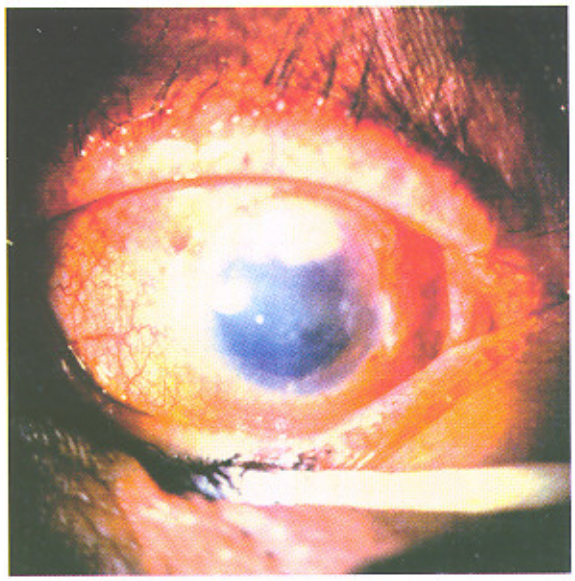

Fig. 1. Herpetic keratouveitis in one of the cases of group B (oral and topical acyclovir)

DISCUSSION

This study has revealed that therapeutic efficiency of administering acyclovir is not significantly different from that of topical acyclovir alone in the treatment of necrotizing herpetic keratoconjunctivitis assessed in terms of anterior chamber reaction, surface area and thickness of corneal infiltration and necrosis, density of corneal lesion, corneal edema, corneal sensation, aided visual acuity, and intraocular pressure. Additionally, the rate of secondary infection and nonpharmacologic therapy is not significantly different in the two groups. The personal characteristics and ophthalmologic findings prior to treatment were identical or showed an insignificant difference in the two groups.

Several studies have been conducted on the treatment of ophthalmic herpes infection. Colin (1993) studied 190 patients with Herpetic Keratitis in France who received oral acyclovir, 200 mg four times daily. It was concluded in his study that the recurrence rate of herpetic keratitis decreases with this method (26). Moszczynska (1992) from Poland studied 44 patients with different forms of ophthalmic herpes who were treated with oral acyclovir, 400 mg five times daily. The therapeutic results were reported to be "satisfactory" in his study (27).

Uchio (1994) from Japan treated different stages of ophthalmic herpes with topical acyclovir or IDU and concluded that severe corneal ulceration, hypopyon, descemetocele and necrotizing keratitis were observed less frequently with acyclovir than with IDU. Additionally, the five-year recurrence rate of herpes infection was lower with topical acyclovir therapy (22). Popa (1994) From Romania stated that acrlovir was the treatment of choice for ophthalmic herpes and could improve the visual acuity of all patients in a short period of time (23). Trichet (1993) from France, studied 17 patients with chronic herpetic uveitis who were treated with oral acyclovir. Satisfactory results were reported and it was stated that longer courses of treatment and higher doses of acyclovir were effective in preventing the recurrence of disease (24).

Rodriguez (1995) studied the effectiveness of oral acyclovir (600-800 mg daily) as a preventive measure in 20 patients with herpetic uveitis. It was concluded that long-term treatment with oral acyclovir was effective in preventing recurrence and decreasing visual loss (28). Collum stated that acyclovir 3% ointment was superior to vidarabine 3% ointment and topical betamethasone in treating disciform keratitis. In another study, he reported that oral acyclovir was successful in healing 21 cases of stromal keratitis during 21 days (8). Van Ganswijk claimed that all 25 cases of stromal keratitis were successfully treated with oral acyclovir during 2-4

weeks (8).

Sanitato (1984) reported that administering oral and topical acyclovir (without steroid therapy) to 17 cases of the herpetic stromal keratitis did not result in healing of disease (13). Schwab (1988) studied 20 patients with epithelial keratitis, stromal keratitis, and uveokeratitis which were refractory to F3T and steriod. It was demonstrated that adding 1 g of oral acyclovir to the drug regimen caused subjective and objective improvement in the patient's condition (12).

Porter administered oral acyclovir, 2g daily and prednisolone 0.05% drop to patients with herpetic disciform keratitis and concluded that this treatment had the same efficacy as acyclovir 3% ointment. It was observed that complete healing occured 25 days after initiating treatment, and both topical and oral forms of acyclovir were successful in relieving epiphora and improving visual acuity (8). Brik (1993) treated two cases of herpetic stromal keratitis with topical and oral acyclovir for a period of 2-5 months. Consequently, penetrating keratoplasty was necessary. After the operation, antiviral therapy with tapering doses of oral acyclovir was continued (19).

Cheng (1995) from China studied the effect of oral acyclovir on two patients with linear endotheliitis over their corneal grafts. In these patients, an episode of migratory KP line and stromal edema, resembling graft rejection was observed on donor and recipient components. Steroid therapy was unsuccessful in relieving the condition, but administering oral acyclovir 200 mg five times daily, with or without acyclovir 3% ointment five times daily, effected considerable improvement in patients' condition (20). Darrel (1991) considers oral acyclovir therapy to be an essential and effective measure in cases of epithelial herpetic keratitis which are refractory to topical treatments and in cases of stromal keratitis, especially cases of keratouveitis which are refractory to steroids and cycloplegics (16).

The studies of HEDS (Herpetic Eye Disease Study) in the United States have been carried out in three stages with randomized, double-blind placebo-controlled design.

The first study was conducted by Wilhelmus et al (1994) to assess the efficacy of topical steroids in the treatment of herpetic stromal keratitis (11). According to this study, topical steroid regimen is far better than placebo in controlling stromal keratitis (8,9,18). The second HEDS study is similar to our study and was carried out by Barron et al (1994) to assess the effect of oral acyclovir in treating stromal keratitis (necrotizing and disciform variants). This study was conducted on 104 patients without epithelial defects or with defects smaller than 1 mm. The selected patients were randomized into two groups of oral acyclovir therapy and placebo treatment. All patients were given prednisolone phosphate 1% drop and F3T.

Follow-up continued for the ten weeks of drug therapy and the six subsequent weeks. No statistically and clinically significant difference was observed in the two groups in the following aspects: the timing of treatment failure, the ratio of refractory patients, the timing of treatment success, and best visual acuity after six months. The only observed difference was better improvement of visual acuity after six months in patients who had taken oral acyclovir. It was concluded that making use of oral acyclovir as an adjunctive therapy for herpetic stromal keratitis in patients who were taking steroids and topical antiviral agents should not be recommended (8,9,10,18).

The third HEDS study was carried out by Dawnson et al (1996) to assess the benefits of the addition of oral acyclovir to a regimen of prednisolone phosphate and topical F3T in herpetic iridocyclitis. The researchers intended to study 104 patients, but during the four-year period of the study, only fifty patients were referred to them. The first group took oral acyclovir, 400 mg five times daily for ten weeks. The second group were given oral placebo together with F3T and topical steroid. Clinical improvement was usually observed after four weeks. The acyclovir concentration in aqueous humor is about one half less with oral administration than with topical therapy, but higher serum drug levels and better intraocular penetration in systemic administration suggests oral acyclovir to be therapeutically effective in herpetic iridocylitis, however the sample size in the study was not large enough to draw a definite conclusion. Nevertheless, administering oral acyclovir in conjunction with antiviral drugs and topical steroids is not without benefit and the possible advantages of acyclovir are revealed after three weeks of follow-up when steroid drugs are gradually tapered (29).

In this study, the effects of acyclovir were studied in the acute phase of the disease and in long-term follow-up. The results of long-term follow-up reveal the effectiveness of oral and topial acyclovir in controlling the disease and prevention of recurrences. The acute condition of the patients with necrotizing keratouveitis who were at risk for losing their eye and the high surface area of necrosis constrained us to administer steroids and cycloplegics and topical acyclovir in both groups. The effects of adding oral acyclovir to this regimen was studied in one group of the patients.

Since no difference was observed in the two groups, oral acyclovir dose not seem to be superior to topical acyclovir in the treatment of necrotizing herpetic keratouveitis. The effects of oral and topical acyclovir in less severe forms of the disease have been studied separately in the above-mentioned studies, but no study has yet been carried out on cases of extensive corneal necrosis. In this study the effects of oral and topical drug are compared in this stage of the disease.

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