HERPES ZOSTER OPHTHALMICUS – ACUTE OCULAR MANIFESTATIONS AND ROLE OF ORAL ACYCLOVIR

Qamar Ul Islam, * Irshad Hussain, ** Lateef Ur Rehman

Combined Military Hospital Jehlum, *PAF Hospital Mianwali, ** Combined Military Hospital Peshawar

ABSTRACT

Objective: To determine the frequency and severity of acute ocular complications in patients of Herpes Zoster Ophthalmicus (HZO) and to evaluate the role of oral Acyclovir in the treatment of HZO.

Study Design: A quasi-experimental study.

Place and Duration of Study: The study was conducted at eye department of CMH Pano Aqil and CMH Peshawar from Jan 2004 to Jun 2006.

Patients and Methods: Thirty Seven patients of HZO were prospectively evaluated for protocol defined ocular manifestations of HZO. Frequency and duration of acute ocular manifestations were analyzed and compared in between those patients who received oral acyclovir within 72 hours of rash onset (Group A, n = 19) and those who received it after 72 hours of rash onset (Group B, n = 18).

Results: The most frequent acute ocular manifestations were conjunctivitis (63% in Gp A; 50% in Gp B), acute epithelial keratitis (37% in Gp A; 39% in Gp B), and anterior uveitis (11% in Gp A; 39% in Gp B). In between group difference in the frequencies of various ocular complications was not statistically significant. However, incidence of overall keratitis, anterior uveitis and glaucoma was more in group B. Moreover, mean duration of acute ocular signs was longer in group B.

Conclusion: The results suggested that early initiation of oral acyclovir treatment (within 72 hours of rash onset) has a beneficial role in limiting the frequency and duration of acute ocular complications of HZO.

Keywords: Herpes Zoster Ophthalmicus, Ocular manifestations, Acyclovir

INTRODUCTION

Herpes zoster is caused by reactivation of dormant Varicella-Zoster virus (VZV) within a sensory nerve ganglion, probably due to alteration in cellular immunity mechanisms [1,2]. Herpes Zoster Ophthalmicus (HZO) refers to involvement of ophthalmic division of trigeminal nerve that occurs in about 10–25% of all cases of zoster [3,4]. Maxillary and mandibular nerve involvement may also occur rarely [5]. Involvement of the side of tip of nose (Hutchinson's sign) supplied by nasociliary branch of ophthalmic nerve, occurring in about one-third of patients correlates significantly with the development of ocular complications [4].

Ocular damage in HZO may presumably occur as a result of direct viral invasion, secondary inflammation, occlusive vasculitis, hypoesthesia and/or altered immunologic mechanisms [4,6]. Advancing age, depressed immune response (HIV infection, malignancy) or immunosuppressive therapy is associated with increased incidence of HZO.

HZO usually begins with a prodrome of influenza like illness, preceded or followed by pre-herpetic neuralgia. This is followed within 3-5 days by cutaneous erythmatous or maculo-papular eruption over the distribution of ophthalmic division of trigeminal nerve that soon become vesiculo-pustular with eventual ulceration, crusting and scarring within few days/weeks [4]. Acute and chronic ocular manifestations and complications of HZO are given in (table-1).

Currently recommended multitude of therapeutic strategies for HZO tailored according to the presentation includes

Correspondence: Major Qamar Ul Islam, Eye Department, Combined Military Hospital, Jehlum
E-mail: qamarulislam@yahoo.com
Received: 12 Aug 2006: Accepted 21 Dec 2006

systemic anti-viral drugs, topical and systemic corticosteroids, topical antibiotics, topical lubricants, cycloplegic drops and analgesics. Oral Acyclovir, 800 mg five times a day for 7-10 days, when administered within 72 hours of onset of rash, reduces the incidence, severity and duration of acute ocular complications, zoster associated pain and decreases the duration of viral shedding along with a beneficial effect on cutaneous lesions [3, 4].

The objectives of this study were to determine the frequency and severity of acute ocular complications of HZO in a hospital based setting and to evaluate the role of oral Acyclovir in the treatment of HZO.

PATIENTS AND METHODS

A quasi-experimental study was conducted at Eye departments of Combined Military Hospital Pano Aqil and Peshawar from Jan 2004 to Jun 2006. 39 consecutive patients with clinically diagnosed HZO were included in this study using non randomized convenience sampling technique. All the patients were either referred directly to Eye OPD or were sent through skin OPD for management of ocular complications. All patients have cutaneous lesions in the distribution of ophthalmic division of trigeminal nerve except one having involvement of maxillary division of trigeminal nerve. Exclusion criteria included significant pre-existing systemic disease; patients on immunomodifying treatment of any type or inability to complete follow up.

Demographic data, ocular manifestations and their duration, presence or absence of nasociliary involvement and oral acyclovir/other treatment regimen were endorsed on a prescribed proforma. Patients were evaluated on presentation, day 3,7,14,21 and one month with an assessment of visual acuity, intraocular pressure measurement, ophthalmic examination by slit lamp biomicroscopy and 90 D slit lamp indirect ophthalmoscopy. Since this study was performed on an intent-to-treat basis, almost all the patients were prescribed oral acyclovir in a dose of 800 mg five times a day for 7-10 days. However, the frequency and severity of ocular complications were analyzed and compared in between the two groups of patients. Group A comprised of those patients who had initiation of oral acyclovir treatment within 72 hours of rash appearance, whereas, Group B included those patients who received oral acyclovir therapy after 72 hours of rash onset or did not received it altogether. During the entire follow up, patients also received other treatment including topical steroids-antibiotic creams, anti-glaucoma drugs, NSAID's and/or therapy for post herpetic neuralgia depending upon the ocular findings and patient's requirements. Statistical analysis was performed on observed data by using SPSS version 10.0. Student 't' test and Fischer exact test were applied and a p-value of <0.05 was considered significant.

RESULTS

Out of 39 patients initially enrolled in this study, two were excluded from the final analysis as they were unable to complete the follow up. There were 28 (76 %) males and 9 (24%) females with most of the patients in 5th and 6th decades of life (fig 1,2). Group A comprised of 19 patients, whereas Group B had 18 patients. Mean age and sex distribution were comparable between two groups (Table 2). The most frequent ocular manifestations were conjunctivitis (63% in Gp A; 50% in Gp B) (p=0.514), acute epithelial keratitis (37% in Gp A; 39% in Gp B) (p=1.000), and anterior uveitis (11% in Gp A; 39% in Gp B) (p=0.062). Involvement of nasociliary nerve (Hutchinson's sign) was found in 6 (16%) patients with all of them having significant intraocular involvement. There was no significant in between group difference in the frequency of various ocular complications recorded within one month of onset of disease except that the frequency of overall keratitis, anterior uveitis, and glaucoma was more in group B (Table 3). An important observation was that the mean duration of acute ocular signs to resolve was longer in group B (19.94 ± 3.83 days) as compared to group A 15.0±3.04 days $p<0.05$ (fig 3).

Table 1: Ocular manifestations of HZO

Ocular manifestations/ complications	Time of onset (Day 0 = rash onset)
Lid odema / mechanical ptosis	Day 0
Conjunctivitis	2-3 days
Episcleritis/Scleritis	One week
Keratitis	
• Acute epithelial keratitis	2 days
• Dendritic keratitis	4-6 days
• Nummular keratitis	10 days
• Disciform keratitis	3 weeks
• Neurotrophic keratitis	months to years
• Mucous plaque keratitis	3-6 months
Anterior uveitis	Within 2 weeks
Glaucoma	Variable
Cranial nerve palsies (III, IV, VI Nerve)	Variable
Optic neuritis	Variable

Table 2: Patient's Demography

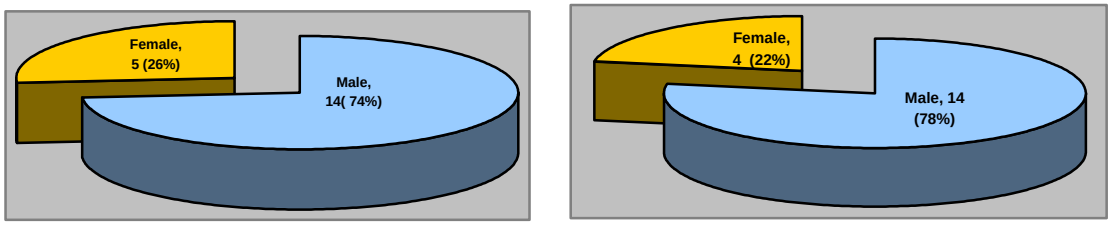
	Group A [n = 19]	Group B [n = 18]	p - value
Mean Age ± SD (years)	46.68 ± 12.03	47.06 ± 12.63	0.914*
Sex, no (%)			
• Male	14 (74%)	14 (78%)	–
• Female	5 (26%)	4 (22%)	0.999

* Not significant

Table 3: Acute ocular complications of HZO (According to treatment groups)

Ocular complications	Gp A no. (%) (n = 19)	Gp B no. (%) (n = 18)	p -value*
Conjunctivitis	12 (63)	9 (50)	0.514
Acute epithelial keratitis	7 (37)	7 (39)	1.000
Dendritic keratitis	2 (11)	2 (11)	1.000
Disciform keratitis	–	2 (11)	0.229
Nummular keratitis	2 (11)	4 (22)	0.404
Anterior uveitis	2 (11)	7 (38)	0.062
Scleritis/episleritis	–	2 (11)	0.229
Glaucoma	1 (5)	5 (27)	0.089
Lid odema/ptosis	10 (52)	8 (44)	0.745

*Fischer exact test



GROUP A **GROUP B**

Fig 1: Sex distribution

DISCUSSION

HZO is a vision threatening disease with severe long term complications that requires appropriate and timely treatment. Male to female ratio in this study was 2.4:1 with peak incidence of HZO in 5th and 6th decades of life. Womack and Liesegang [7], Severson et al [8], and Tyring et al [9] in their studies showed a female preponderance and peak incidence in 6th to 7th decades of life.

This is differed by Yoshida et al [10] in their study showing male predominance. Male predominance in our study was probably related to the social barriers and limited access of female patients to the hospital.

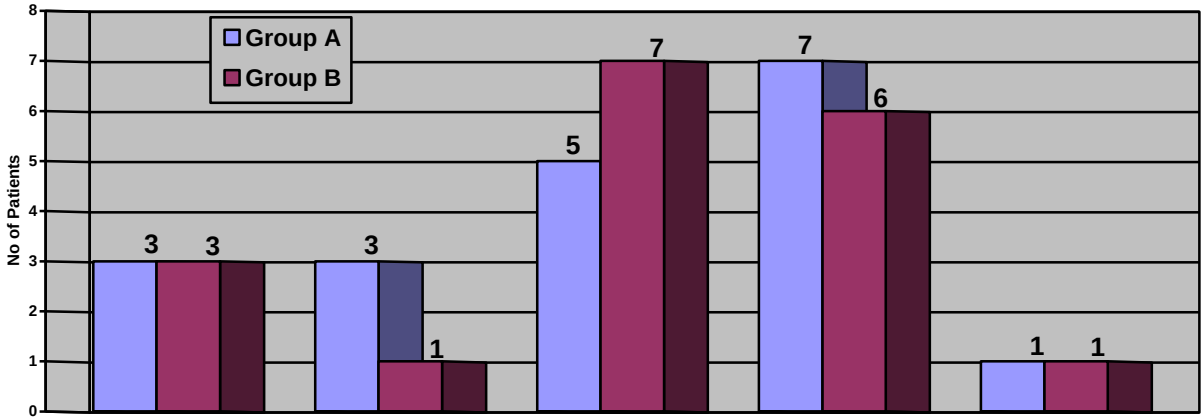


Fig 2: Age spectrum

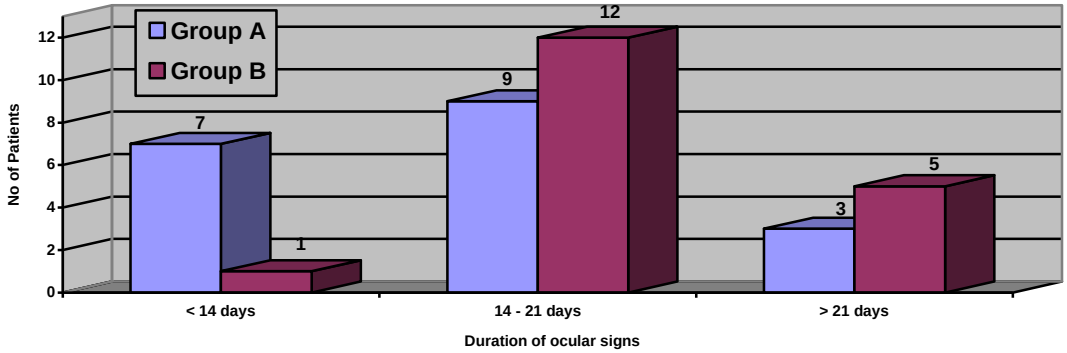


Fig 3: Duration of acute ocular manifestations

It is quite difficult to directly compare our data with other studies due to variability in study designs, duration, outcome measures and definition of ocular manifestations. Most common acute ocular manifestations of HZO observed in this study were acute conjunctivitis and superficial corneal involvement. This was comparable to the results of studies by Liesegang [11], (corneal involvement 64% cases), Colin et al [12], (conjunctivitis 52%, superficial keratitis 48%) and Womack and Liesegang [7], (keratitis 54%). Sultan and Farooq [13] prospectively evaluated 15 patients of HZO for ocular complications and found conjunctival congestion in 73.33%, punctate epithelial keratitis in 73.33% and glaucoma in 20% of patients. Overall frequency of anterior uveitis was 24% in our study, whereas an incidence of 25% and 30% respectively were observed in studies by Tyring et al [9] and Harding and Porter [14] respectively.

Systemic antiviral therapy administered early in the course of disease (within 72 hours of rash onset) has been found to speed up resolution of skin lesions, reduce viral shedding and decrease the incidence of dendritic and stromal keratitis as well as anterior uveitis [3]. This study also reflected a lower frequency, severity and duration of acute ocular complications of HZO like acute keratitis, anterior uveitis and glaucoma in patients who had initiation of oral acyclovir therapy within 72 hours of rash onset. These beneficial effects of oral acyclovir also reduce the chances of subsequent visual loss and other adverse outcomes.

Cobo et al [15] prospectively evaluated 71 patients of HZO treated with either oral acyclovir 600 mg five times a day or with placebo. They found that oral acyclovir significantly reduces the incidence and severity of the ocular complications of HZO including dendritic and stromal keratitis, anterior uveitis and keratic precipitates. Studies by Hoang-Xuan et al [16] and Harding et al [14] also found lower ocular complication rates in patients treated with

oral and topical acyclovir as compared to placebo groups.

One of the limitations of this study was relatively short duration of follow up as our focus was on the evaluation of acute ocular manifestations. But this is an ongoing study with further analysis of other aspects of disease like chronic ocular complications, post herpetic neuralgia and visual outcome in process.

CONCLUSION

Timely diagnosis and appropriate treatment of HZO with an early referral to an ophthalmologist in case of ocular involvement is essential in limiting visual morbidity. Oral acyclovir therapy when began within 72 hours of rash onset is most effective in preventing and limiting ocular complications.

REFERENCES

1. Tunsuriyawong S, Puavilai S. Herpes zoster, clinical course and associated diseases: a 5-year retrospective study at Tamathibodi hospital. J Med Assoc Thai 2005; 58: 5: 678-81
2. Kost RG, Straus SE. Postherpetic Neuralgia–Pathogenesis, treatment and prevention. N Engl J Med 1996; 335: 32-42
3. Shaikh S, Christopher N. Evaluation and Management of Herpes Zoster Ophthalmicus. Am Fam Physician 2002; 66: 1723-32
4. Kanski JJ. Cornea. In: Kanski JJ. Clinical Ophthalmology. 5th ed. Oxford: Butterworth-Heinemann; 2003: 96-143
5. Jain S, Rathore MK. Maxillary Zoster with Corneal involvement. Indian J Ophthalmol 2004; 52: 323-4
6. Karbassi M, Raizman MB, Schuman JS. Herpes Zoster ophthalmicus. Survey of ophthalmol 1992; 36(6): 395-410
7. Womack LW, Liesegang TJ. Complications of Herpes zoster Ophthalmicus. Arch Ophthalmol 1983; 101: 42-45
8. Severson EA, Baratz KH, Hodge DO, Burke JP. Herpes zoster ophthalmicus in olmsted county, Minnesota. Have systemic antivirals made a difference? Arch Ophthalmol 2003; 121: 386-90
9. Tyring S, Engst R, Corriveau C, Robilland N, Trottier S, Slycken SV, et al. Famciclovir for ophthalmic zoster: a randomized acyclovir controlled study. Br J Ophthalmol 2001; 85: 576-81
10. Yoshida M, Hayasaka S, Yamada T, Yanagisawa S, Hayasaka Y, Nakamura N, et al. Ocular findings in Japanese patients with Varicella-Zoster virus infection. Ophthalmologica 2005; 219: 272-75
11. Liesegang TJ. Corneal complications from herpes zoster ophthalmicus. Ophthalmology 1985; 92: 316-24
12. Colin J, Prisant O, Cochener B, Lescade O, Rolland B, Hoang-Xuan T. Comparison of the efficacy and safety of valaciclovir and acyclovir for the treatment of herpes zoster ophthalmicus. Ophthalmology 2000; 107: 1507-11
13. Sultan M, Farooq A. Ocular complications of herpes zoster ophthalmicus. Professional Med J 1999; 6(2): 238-43
14. Harding SP, Porter SM. Oral acyclovir in Herpes zoster ophthalmicus. Curr Eye Res 1991; 10: 177-82
15. Cobo LM, Foulks GN, Liesegang TJ. Oral acyclovir in the treatment of acute herpes zoster ophthalmicus. Ophthalmology 1986; 93: 763-70
16. Hoang-Xuan T, Buchi ER, Herbort CP. Oral acyclovir for herpes zoster ophthalmicus. Ophthalmology 1992; 99: 1062-70