Original Article

Clinical efficacy of oral and topical acyclovir in herpes simplex virus stromal necrotizing keratitis

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Purpose: To evaluate the efficacy of systemic and topical antiviral therapy in the treatment of active herpes simplex virus (HSV) necrotizing stromal keratitis (NSK). **Design:** Prospective interventional case series. **Methodology:** Patients with a diagnosis of HSV NSK based on history and clinical findings were enrolled in the study. A standard protocol was used for microbiologic investigations. Ten weeks regime of systemic acyclovir and 2 weeks of topical acyclovir was given. Complete ophthalmic examination was performed at every visit. Outcome measures were a reduction in the area of infiltration and improvement in visual acuity. **Results:** Fifteen patients were enrolled in the study. The mean age of presentation was 51.53 years. The duration of symptoms at presentation ranged from 2 to 8 weeks. HSV1 DNA polymerase chain reaction was positive in 70% cases of those tested. Area of infiltration at trial entry and at the end of 2 weeks of antiviral treatment reduced significantly (P = 0.007). All patients showed a complete resolution of keratitis at the end of study. **Conclusion:** Topical and systemic acyclovir for treatment of NSK facilitates healing of ulceration. Topical steroids after initial antiviral therapy are safe and decreases inflammation and improve visual recovery. Early initiation of therapy has better outcomes as compared to late presentations.

Key words: Efficacy, herpes simplex virus, necrotizing stromal keratitis, oral acyclovir, topical acyclovir

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.182940

Quick Response Code:

Herpes simplex virus (HSV) keratitis is one of the major causes of infectious blindness in the developed countries. It has been estimated that nearly 500,000 people in the USA are affected with ocular HSV.[1] The impact of the disease in developing nations is currently unknown, although a study conducted by Kaur *et al*. in North India estimated the incidence of HSV1 as 33.3%.[2] Over 95% of ocular herpes is caused by HSV1, out of which HSV stromal keratitis accounts for only 2% of initial presentation, yet it is the cause of 20–61% of recurrent disease.[3] HSV stromal keratitis can clinically manifest either as necrotizing or immune mediated- nonnecrotizing keratitis. The diagnosis of necrotizing stromal keratitis (NSK) is often delayed and corneal perforation, and visual morbidity is common.[3] Herpetic Eye Disease Study (HEDS) revealed the incidence of NSK to be 7%, immune-mediated nonnecrotizing keratitis to be 88% and mixed type to be 5% of the stromal disease.[4] The study also mentioned that insufficient numbers of patients with NSK were included to comment on the effectiveness of therapy for NSK disease. The two forms of the stromal disease have different etiology as HSV1 DNA antigen and even intact live virus have been recovered from NSK while the nonnecrotizing form is essentially immune mediated.[5]

There is a need for recognizing NSK as a rare, but distinct group of HSV stromal keratitis and to develop a treatment algorithm for its management. This study aims to evaluate the efficacy of systemic and topical antiviral therapy in the treatment of active HSV NSK.

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Manuscript received: 02.07.15; Revision accepted: 22.02.16

Methodology

Study design

Prospective interventional case series conducted at a tertiary eye care hospital from April 2013 to April 2014. The study was conducted in compliance with Declaration of Helsinki. Study was approved by the Institutional Ethics Committee. Inform consent was taken from each enrolled subject.

Patients aged more than 18 years with a diagnosis of active HSV NSK were enrolled. Ulcer measuring more than 2 mm^2 and involving more than one-third of corneal stroma with an overlying epithelial defect were included.

Patients were excluded if they had been treated with antiviral therapy and/or topical or systemic steroids within the previous 6 weeks. Culture positive bacterial, fungal, or parasitic infections and patients with known allergy to oral or topical acyclovir were excluded from the study. Pregnant and lactating women and patients with renal insufficiency were also excluded from the study. Patients who had undergone corneal surgery or any ocular surgery in the preceding 6 months were also excluded.

Study protocol

The diagnosis of HSV NSK was based on history and clinical findings. The demographic profile, laterality and duration of

Cite this article as: Dutt S, Acharya M, Gour A, Sapra N, Chauhan L, Mathur U. Clinical efficacy of oral and topical acyclovir in herpes simplex virus stromal necrotizing keratitis. Indian J Ophthalmol 2016;64:292-5.

disease prior to presentation were recorded. The patients were classified as early presentation when the duration of disease was less than 6 weeks and as late presentation when more than 6 weeks duration. History of prior treatment and diagnosis of the keratitis was recorded. History of recurrent episodes of keratitis, any exacerbating or precipitating factors, and any associated systemic illness was recorded.

The diagnosis of NSK was clinically based on the presence of thinning, ulceration, and dense infiltration of the stroma, accompanied by an overlying epithelial defect with minimal discharge. The presence of an old scar and superficial or deep vascularization was recorded. Patient's symptoms, visual acuity, conjunctival injection, stromal edema, size of infiltration, and severity of corneal thinning were evaluated on every visit. The area of stromal infiltration was measured according to HEDS protocol.[6] Complete ophthalmic examination was performed by a single cornea specialist at baseline, day 3 and every week thereafter until 10 weeks. Photo documentation of each case was done. A standard protocol was used for the initial microbiologic investigations for all patients. Corneal scrapings were sent for HSV polymerase chain reaction (PCR).[7] Patients received a 10 weeks regimen of oral acyclovir 400 mg 5 times/day (Acivir, Cipla Ltd, India) and topical acyclovir eye ointment 5 times/day (Acivir, Cipla™) for 2 weeks. Diluted topical prednisolone sodium phosphate eye drops in buffered isotonic aqueous solution (0.125% Predforte™, Allergan, Irvine, CA, USA) was commenced in tapering doses (starting dose of 4 times/day).

Primary outcome measure was a response to therapy which was clinically assessed by comparing the size of infiltrate at trial entry and after 2 weeks of systemic and topical antiviral treatment. Data were analyzed using SPSS software version 17 (IBM, USA). $P \leq 0.05$ was considered statistically significant. Secondary outcome measure was improvement in best-corrected visual acuity from baseline to end of 10 weeks. Any surgical intervention or adverse incident occurring during the course of therapy was recorded to assess safety of the treatment. Scarring with an intact epithelium was considered as a healed keratitis.

Treatment failure was considered in cases where there was an increase in the area of infiltrate, appearance of fresh infiltrate, <10% decrease in the stromal keratitis or corneal perforations requiring keratoplasty within first 2 weeks. Cyanoacrylate tissue adhesive application for management of extreme thinning was noted as a surgical intervention. However, these patients continued to remain in the study and response to therapy was recorded.

Results

Fifteen patients were enrolled in the study. Eleven (74%) were male and four (26%) were female. Two patients were lost to follow-up. The mean age of the patient was 51.53 years (range: 30–80 years). Ten patients showed predilection for the left eye (72.92%) and three patients for the right eye (23.08%). The duration of symptoms at presentation ranged from 2 to 8 weeks. Eight patients (61.5%) were classified as early presentation and five patients (38.5%) as late presentation.

Nine (69.23%) out of 13 patients had a history of recurrence. Stress was the most common risk factor (61.54%). Systemic illness in the form of fever and respiratory infection was recorded in 15.39%. Three patients (23.0%) had no association for any risk factor.

All patients showed sterile culture on microbiological examination. Three eyes had Gram-positive cocci on smear examination. HSV1 DNA PCR was done for all cases out of which 11 were positive (74%).

The area of infiltration at presentation ranged from 2 to 31 mm² with a mean of 8.52 mm² (standard deviation [SD] = 8.19 mm²). Three patients (23.08%) had up to one-third thinning of the corneal stroma and five patients (38.46%) had thinning up to two-third corneal stroma and rest five (38.46%) had severe thinning more than two-third corneal stroma.

After 2 weeks of antiviral therapy, the area of infiltration ranged from 1 to 16 mm², with a mean of 5.12 mm² (SD = 4.62 mm²). Area of infiltration at trial entry and at the end of 2 weeks of antiviral treatment was statistically significant ($P = 0.007$). Ten patients (76.9%) showed complete resolution of the epithelial defect at 2 weeks. Figs. 1-3 depict photographically the response to therapy in three patients.

Three eyes (23.08%) developed spontaneous perforation within the first 2 weeks. These patients were advised cyanoacrylate tissue adhesive application with bandage contact lens. All three had prolonged the duration of presentation (more than 6 weeks), more than two-third corneal thinning and more than 8.1 mm² area of infiltration. These patients responded well to antiviral therapy after application of tissue adhesive. On removal of tissue adhesive at 6 weeks, all three cases showed a response to therapy.

Visual acuity (logMAR) at presentation ranged from 2.20 to 0.48 with a mean of 1.75 (SD = 0.508). At the end of 2 weeks, visual acuity ranged from 0.78 to 2.20 logMAR with a mean of 1.44 (SD = 0.41). At the end of 10 weeks, visual acuity ranged from 1.40 to 0.48 with a mean of 1.087 (SD = 0.387). The improvement in visual acuity from presentation up to 2 weeks was not statistically significant ($P = 0.06$); however, it was statistically significant at the end of 10 weeks ($P = 0.003$).

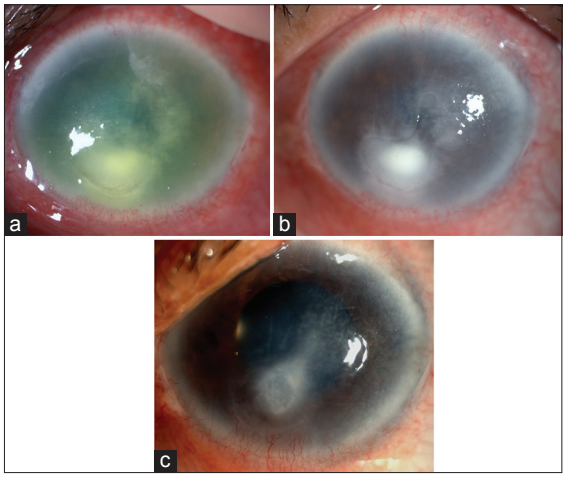

Figure 1: (a) Patient at presentation (9 mm²). (b) Patient on therapy at the end of 2 weeks (5 mm²). (c) Image showing complete resolution at 10 weeks

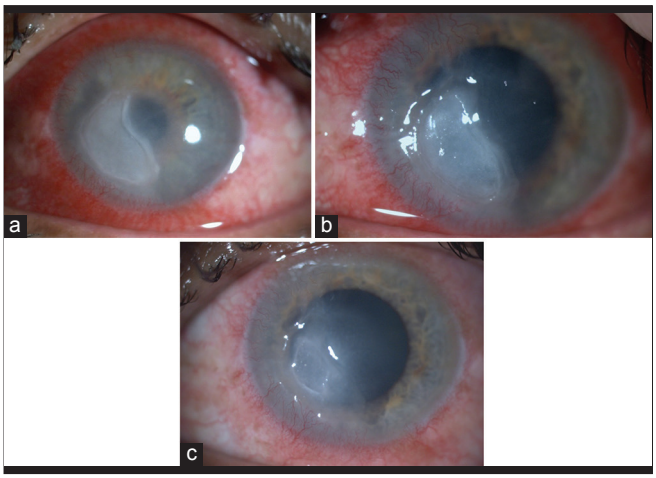

Figure 2: (a) Patient at presentation (31 mm²). (b) At the end of two weeks (16 mm²). (c) Image showing complete resolution at 10 weeks

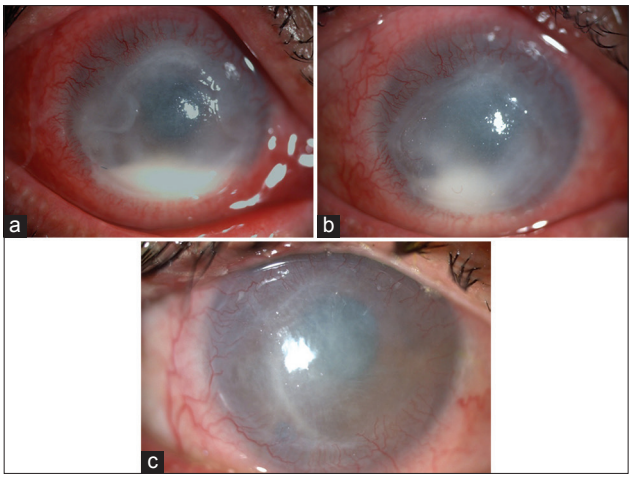

Figure 3: (a) Patient at presentation (19.5 mm²). (b) At end of 2 weeks (13.5 mm²). (c) Image showing complete resolution at 10 weeks

After initiation of topical steroid therapy at the end of 2 weeks, all patients showed symptomatic improvement. There was a decrease in conjunctival injection, pain, and edema. No patient deteriorated after initiation of topical steroid therapy. At the end of 10 weeks, all patients presented with a vascularized corneal scar indicating the complete resolution of keratitis and response to therapy.

Discussion

This study shows that topical and systemic acyclovir for treatment of NSK facilitated healing of ulceration. This was clinically demonstrated by healing of epithelial defect and reduction of stromal infiltration. Addition of topical steroids after initial antiviral therapy decreased inflammation and improved visual recovery. Early presentation and initiation of therapy had better outcomes as compared to late presentations.

The HEDS did not give clear recommendation for treatment of NSK.[4] NSK, in contrast to immune-mediated stromal keratitis and stromal edema due to HSV endotheliitis is essentially an infective disease with a demonstration of live virus in the corneal stroma.[5,8] This study confirmed the presence of live virus in this disease entity with 74% of the samples showing HSV1 DNA in PCR in corneal scraping.

The rationale to use systemic acyclovir for treatment of NSK was based on evidence in the literature that therapeutic concentrations of the drug are present in the plasma following oral administration.[9] The HEDS study also showed a beneficial response to systemic acyclovir in treatment of herpetic uveitis, another condition where the live virus has been demonstrated.[10] This study demonstrated that systemic acyclovir in addition to topical antiviral therapy is effective in treatment of NSK. There was a significant resolution of stromal infiltration within 2 weeks of initiation of therapy.

Topical steroids alone may lead to local immunosuppression and facilitate virus replication.[8] However, steroids have a beneficial role in reducing the overall inflammation, discomfort, and pain of the patient. This has also been seen in this study where after initiation of topical steroids all patients showed symptomatic improvement during the course of the trial. Corneal clarity improved with steroids resulting in an improvement in visual acuity.

In our study, the average onset of symptoms to diagnosis was 2.5 weeks and 8 out of 13 patients were being treated as suppurative keratitis. This study demonstrated that early diagnosis and initiation of treatment leads to better outcomes. Three cases ended up with corneal perforation within the first 2 weeks of trial. All three patients presented late, and with more than two-third stromal thinning at enrollment of study. The regime of systemic and topical acyclovir therapy was not effective in halting the progression to perforation, in cases with extreme thinning. All patients underwent cyanoacrylate tissue adhesive for tectonic support in this group, while systemic acyclovir facilitated eradication of infection.

NSK is the least common but most visually debilitating HSV keratitis. Significant improvement of visual acuity was noted in the majority of cases in this study. However, this improvement was significant at the end of 10 weeks, during this period, topical steroid drops were also given. Low-dose topical steroid therapy did not have any side effects in our study. It is unclear from this study whether only antiviral therapy alone would have resulted in similar outcomes. This study shows a beneficial effect of combination therapy of topical and systemic acyclovir in the treatment of NSK. A randomized, controlled trial is required to determine the beneficial effect of topical acyclovir and oral acyclovir alone.

Conclusion

NSK is an uncommon but distinct clinical entity in the varied presentations of ocular HSV. The disease can have extended periods of morbidity and if left untreated can have a poor visual outcome. This study suggests a treatment algorithm for the management of NSK.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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