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Original Article

Corneal sensation and ocular surface parameters in patients with unilateral herpetic epithelial keratitis

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Abstract

Aim: To compare of the affected eyes of the patients with unilateral herpetic keratitis with their fellow eyes and the healthy controls in terms of ocular surface parameters and corneal sensation.

Materials and Methods: Both eyes of the consecutive patients with a PCR-proven diagnosis of unilateral chronic herpetic epithelial keratitis and the left eyes of age- and gender-matched healthy controls were included in the study. Schirmer's test, tear break-up time (TBUT), corneal sensation, and tear osmolarity were investigated in all of the patients.

Results: Forty-two eyes of 21 patients with unilateral herpetic keratitis and twenty-one eyes of 21 healthy controls who had no ocular pathology were included in the study. While the mean tear osmolarity of the eyes with herpetic keratitis was 317.3±15.6 mOsm/L, it was 313.2±16.1 mOsm/L for the fellow eyes, and 302.6±11.9 mOsm/L for the healthy eyes (p=0.002). Both herpetic eyes and fellow eyes had significantly higher tear osmolarity and lower TBUT values in comparison to the healthy controls (osmolarity: p=0.002 and p=0.03, and TBUT: p<0.001 and p=0.021, respectively). While there was no significant difference between the fellow eyes and healthy eyes in terms of central and peripheral corneal sensation (p=0.4 and p=0.09, respectively), herpetic eyes had lower central and peripheral corneal sensation in comparison to the fellow eyes and healthy controls.

Conclusion: This study showed that both the affected and fellow eyes of the patients with unilateral herpetic epithelial keratitis are affected in terms of dry eye without any significant loss in the corneal sensation of the fellow eye.

Keywords: Herpetic keratitis; unilateral keratitis; epithelial keratitis; tear osmolarity; corneal sensation; dry eye

INTRODUCTION

Herpes simplex virus (HSV) keratitis is one of the most common etiologies of unilateral blindness (1,2) and one of the most frequent reason for infectious keratitis in the developed countries (3–5). Herpes virus is a latent DNA virus that shows retrograde axonal transport (6,7). Unilateral involvement of herpetic keratitis is observed in most of the patients, whereas bilateral involvement has been reported to be between 1.3-12% and is observed mainly in the immunocompromised or atopic patients (1,8).

Herpes simplex keratitis (HSK) might present as neurotrophic keratopathy, epithelial keratitis, immune and necrotizing stromal keratitis, or endotheliitis (9). HSK can show recurrences and after each recurrence, corneal sensation loss with varying severity causing neurotrophic keratopathy is observed. HSK can cause damage in the corneal subbasal nerve plexi leading to loss in corneal sensation and disturbance in the normal blink reflex. These corneal changes can lead to corneal epithelial injury, secondary corneal infections, and corneal melting (10,11).

Previous studies showed that the contralateral unaffected eyes of the patients with herpetic keratitis had worse ocular surface parameters and reduced corneal nerve density without any change in corneal sensation in comparison to the controls (12,13). Furthermore, the affected eyes of the herpetic keratitis patients have been shown to have findings of corneal nerve regeneration after a means of 37 months (14). Although decreased corneal sensation and reduced corneal nerve density were shown in herpetic

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uveitis and keratitis patients (15), to date, no study was conducted for evaluating both the corneal sensation and ocular surface parameters in the herpetic keratitis patients when the disease is limited only to the epithelial layer.

In this study, comparison of the affected eyes of the patients with unilateral herpetic epithelial keratitis with their fellow eyes and the healthy controls in terms of tear osmolarity, Schirmer score, tear break-up time (TBUT) value, and corneal sensation was aimed.

MATERIAL and METHODS

The consecutive patients with a PCR-proven diagnosis of unilateral chronic (infection has occurred in a period longer than 10 weeks) herpetic epithelial keratitis were included in the study. Ethical approval was obtained from the local institutional board. Informed consent was obtained from the patients or their legal guardians. The research was conducted according to the tenets of the Helsinki declaration. The age, gender, and duration of follow-up of the patients were evaluated. Schirmer's test, tear break-up time (TBUT), corneal sensation, and tear osmolarity were investigated in all of the patients.

In the study group, patients with a history of any corneal pathology or intraocular surgery, lid pathologies including blepharitis, nasolacrimal system pathologies, ocular surface disorders, and the use of systemic medication that may interfere normal tear secretion or function (medications with antimuscarinic effects, etc.) in the year preceding the study were excluded from the study. The patients with atopy or bilateral herpetic corneal involvement were also excluded. Patients without any history of ocular pathology, intraocular surgery, and the use of systemic medication that may interfere normal tear secretion or function were included as healthy controls. Left eyes of each healthy control were included in the study.

Detailed slit-lamp examination was performed for all of the patients and controls. The diagnosis of HSK was made according to characteristic epithelial dendritic lesions of epithelial HSV keratitis and PCR analysis of corneal scrape specimens.

TBUT was recorded as the time interval between the last blink after fluorescein dye staining (non-preserved 2% sodium fluorescein) and the appearance of the first corneal black spot. Three measurements were taken from each eye and the average of these measurements was calculated as recommended by the DEWS report 2007 (16).

Schirmer-I test (without anesthesia) was performed with the standard filter paper 30 minutes after TBUT. Schirmer test sterile strips were placed in the lower outer fornix of both the eyes. After five minutes with the eyes closed, the strip was removed from the eye and the length of wetting was measured.

Tear osmolarity of the patients was measured using TearLab Osmolarity System (TearLab Corp, San Diego, CA). Without topical anesthesia, with a single-use test card, less than 50 nl of tear fluid is passively and non-invasively collected by capillary action. Tear osmolarity measurement was performed for both eyes of the patients. The calibration of the system was verified on every study day by testing reusable electronic check cards (provided by the manufacturer as a quality-control procedure).

Central and peripheral corneal sensation were measured bilaterally with a Cochet-Bonnet esthesiometer (Luneau Ophthalmologie, Chartres, France) between 10 AM and 12 AM. The esthesiometer was always used in the unaffected fellow eye first. This test mechanically stimulates corneal nerves by pressing a nylon filament (6 cm in length) against the anterior corneal surface. Shortening of the nylon filament 0.5 cm was done if a positive response is not obtained. The longest filament length resulting in a positive response was considered the corneal sensitivity threshold, which was verified three times. Peripheral corneal sensation was measured on four peripheral quadrants and the average of these measurements was calculated.

Statistical analysis

For the comparison of means between two groups, a Mann Whitney U test was used and for the comparison of means between three groups Kruskal Wallis test was used as an omnibus test. For the post hoc analysis of the results, pairwise comparison with Mann Whitney U test with Bonferroni correction was utilized. A chi square test was used for the comparison of ratios. SPSS 21.0 was used for all statistical analyses and p values below 0.05 were accepted as statistically significant.

Results

Forty-two eyes of 21 patients with unilateral herpetic keratitis and twenty-one eyes of 21 healthy controls who had no ocular pathology were included in the study. The mean age of the patients with herpetic keratitis was 43±20.1 years and it was 39.3±15.6 years for the healthy controls (p=0.55). Female: Male ratio was 3:4 in both groups (p=1.0). The mean follow-up duration for the study group was 55.2±79.9 months.

While the mean tear osmolarity of the eyes with herpetic keratitis was 317.3±15.6 mOsm/L, it was 313.2±16.1 mOsm/L for the fellow eyes, and 302.6±11.9 mOsm/L for the healthy eyes (p=0.002) (Table 1). While herpetic eyes showed comparable results with the fellow eyes (p=1.0), both herpetic eyes and fellow eyes had significantly higher tear osmolarity values (p=0.002 and p=0.03, respectively).

The mean central corneal sensation was found to be 2.7±1.7 cm for the herpetic eyes, 5.3±0.8 cm for the fellow eyes, 5.7±0.4 cm for the healthy eyes (p<0.001). The mean peripheral corneal sensation was found to be 3.7±1.3 cm for the herpetic eyes, 5±1.2 cm for the fellow eyes, 5.7±0.3 cm for the healthy eyes (p<0.001). While there was no significant difference between the fellow eyes and healthy eyes in terms of central and peripheral corneal sensation (p=0.4 and p=0.09, respectively), herpetic eyes had lower central and peripheral corneal sensation in comparison to the fellow eyes and healthy controls (Table 2).

Table 1. Comparison of the tear function and corneal sensation with Kruskal Wallis test in three groups (the herpetic eyes, fellow eyes, and healthy controls)

	Herpetic eyes	Fellow eyes	Control group	p value
Schirmer (mm)	11.9±7.5	16.7±10	25.2±9.3	<0.001*
TBUT (sec)	5.1±3	7.3±4	10.4±3.1	<0.001*
Osmolarity (mOsm/L)	317.3±15.6	313.2±16.1	302.6±11.9	0.002*
Central Corneal Sensation (cm)	2.7±1.7	5.3±0.8	5.7±0.4	<0.001*
Peripheral Corneal Sensation (cm)	3.7±1.3	5±1.2	5.7±0.3	<0.001*

p<0.05, statistically significant; TBUT: Tear break-up time

Table 2. Pairwise comparison of the herpetic eyes, fellow eyes, and healthy controls with Mann Whitney U test

	p values		
	Herpetic Eyes vs Fellow Eyes	Herpetic Eyes vs Control	Fellow Eyes vs Control
Schirmer (mm)	0.335	<0.001*	0.051
TBUT (sec)	0.23	<0.001*	0.021*
Osmolarity (mOsm/L)	1.0	0.002*	0.03*
Central Corneal Sensation (cm)	<0.001*	<0.001*	0.4
Peripheral Corneal Sensation (cm)	0.01*	<0.001*	0.09

*p<0.05, statistically significant; TBUT: Tear break-up time

The mean Schirmer test results were 11.9±7.5 mm for the herpetic eyes, 16.7±10 mm for the fellow eyes, and 25.2±9.3 mm for the healthy controls (p<0.001). While herpetic eyes had significantly lower Schirmer scores in comparison to the healthy controls (p<0.001), when the fellow eyes were compared with the herpetic eyes and healthy controls in terms of the Schirmer scores, no significant difference was observed (p=0.335 and p=0.051, respectively).

While the mean TBUT was 5.1±3 sec for the herpetic eyes, it was 7.3±4 sec for the fellow eyes, and 10.4±3.1 sec for the healthy controls (p<0.001). Consistent with the tear osmolarity findings, despite no significant difference between herpetic and fellow eyes (p=0.23), both herpetic eyes and fellow eyes showed significantly lower TBUT values in comparison to the healthy eyes (p<0.001 and p=0.021, respectively).

DISCUSSION

Herpetic keratitis is a common cause of neurotrophic keratopathy (10). It can involve all of the corneal layers as well as it can be limited only to the epithelial layer (17). In this study, affected eyes of the patients with unilateral herpetic epithelial keratitis were compared with their fellow eyes and the healthy controls in terms of tear osmolarity, Schirmer score, tear break-up time (TBUT) value, and corneal sensation. It was found that both the affected and fellow eyes of the patients with unilateral herpetic epithelial keratitis are affected in terms of dry eye without any significant loss in the corneal sensation of the fellow eye.

The finding of dry eye in both eyes without no significant change in the corneal sensation of the fellow eyes can be explained with diminished blink reflex as a result of decreased corneal sensation in the affected eye leading to disruption in the tear film stability. Because there is a consensual corneal reflex stimulating the blink reflex in the contralateral eye. Consistent with our findings, Hamrah et al. and Moein et al. found a significant decrease in the corneal sensation in the affected eyes of the patients with HSK without a change in the contralateral eyes (13,14). However, both studies showed reduced corneal nerve density in both eyes of the patients with HSK. Furthermore, Moein et al. showed that the affected corneas of the patients with epithelial HSK were not able to regain their sensation loss even after a mean of 37 months despite the proof of nerve regeneration in confocal microscopy. However, they did not present any data regarding dry eye to correlate their findings.

Although the present study showed decreased BUT values in the contralateral unaffected eyes of the patients with HSK, no change was shown in Schirmer values. In a study, Jabbarvand et al. found that both Schirmer and TBUT values were affected negatively in the contralateral eyes of the patients with herpetic keratitis or neurotrophic ulcer.

The difference might be related to the inclusion of stromal HSK and neurotrophic ulcer rather than epithelial HSK.

In a recent study, Zemaitiene et al. compared the corneal sensation of the affected eyes of the patients with herpes simplex keratitis or uveitis with their unaffected eyes. They also compared the corneal sensation of the epithelial, stromal, and endothelial HSK patients. The authors showed that the affected eyes of the stromal HSK patients had significantly lower corneal sensation in comparison to those of the epithelial HSK patients. They also showed that after six months of follow up subbasal nerve fiber parameters and corneal sensation increased in comparison to the contralateral eye despite no change in the mean nerve density, the total number of nerves, the number of main nerve trunks, and the number of branches (15). Thus, contrary to Moein et al., they claimed a clinically significant corneal nerve regeneration in the affected eyes of the patients with HSK. However, major limitation of their study is the lack of a healthy control group limiting the extent of their findings. They also did not correlate their findings with dry eye parameters. However, their finding of higher corneal sensation in the epithelial keratitis might explain unchanged Schirmer in the contralateral eyes as observed in the present study.

Limitations of the present study are the lack of different herpetic keratitis groups and confocal microscopy data, and relatively low number of patients.

CONCLUSION

In conclusion, this study showed that when herpetic keratitis is limited even in the epithelial layer, both the affected and fellow eyes of the patients are affected in terms of dry eye without any significant loss in the corneal sensation of the fellow eye. The corneal sensation loss in the affected eye might be linked to diminished blink reflex leading to dry eye in both eyes. However, these results should be compared with other forms of herpetic keratitis with future studies focused both on dry eye parameters and corneal nerve regeneration for a better understanding of the changes in the cornea after herpetic keratitis.

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