A Novel Grading Method for Superficial Punctate Keratopathy Magnitude and Its Correlation With Corneal Epithelial Permeability

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Objectives: To propose a novel grading method for superficial punctate keratopathy (SPK) magnitude and to examine the quantitativeness of the method.

Methods: In 351 eyes diagnosed as having dry eye syndrome, SPK was graded as follows. After fluorescein staining, the total sum of the area of SPK was graded from A0 through A3, and the density was graded from D0 through D3. The grading was represented as the combination of the area and density grades. The correlation between the SPK grade and the corneal epithelial permeability to fluorescence, measured using an anterior fluorophotometer, was analyzed in the 351 eyes.

Main Outcome Measures: The correlation between the fluorescein concentration in the cornea and the sum of the area and density grades.

Results: The higher the density and area grades, the higher the fluorescein concentration, except for A3D2. There was a clear exponential correlation between the sum of the area and density grades and the fluorescein concentration in the cornea, measured using an anterior fluorophotometer. The regression curve was $y = 61.2e^{0.36x}$, where $y$ is the fluorescein concentration (nanograms per milliliter), and $x$ is the sum of the area and density grades ($P<.001$).

Conclusions: The SPK grade is positively correlated with the corneal epithelial permeability to fluorescence, measured using an anterior fluorophotometer. Our results indicate that this grading method can be clinically useful.

Arch Ophthalmol. 2003;121:1537-1539

Superficial punctate keratopathy (SPK) develops in patients with dry eye syndrome, meibomian gland dysfunction, neurotrophic and exposure keratopathy, and in those who wear contact lenses. Because there is no established grading method for SPK magnitude, it is sometimes hard to recognize the time course of the changes in SPK magnitude and to evaluate the effect of drugs used to treat SPK, or the adverse effects of drugs that induce SPK. Jones classified superificial keratitis into punctate epithelial keratitis and punctate epithelial erosion, depending on the presence or absence of inflammation. His classification, however, did not determine the SPK magnitude in terms of SPK area and density. In a previous study, we proposed an SPK grading system to facilitate a quantitative description of SPK and to evaluate the validity of this method, which uses the area and density of SPK as parameters. The current study examines our grading system in 351 eyes diagnosed as having dry eye syndrome.

In this study, we examined the quantitativeness of the method and the correlation between the SPK grade and the corneal epithelial permeability to fluorescence, measured using an anterior fluorophotometer, in 351 eyes diagnosed as having dry eye syndrome.

METHODS

Superficial punctate keratopathy was graded using the area and density of the lesion as parameters. After fluorescein staining, the total sum of the area of SPK was graded as A0 when there was no punctate staining, A1 when the area occupied less than one third of the cornea, A2 when the area occupied one third to two thirds of the cornea, and A3 when the area occupied greater than two thirds of the cornea. The density was graded as D0 when there was no punctate staining, D1 when the density was sparse, D2 when the density was moderate, and D3 when the density was high and the lesions overlapped. The combination of the area and density grade represented the final grade, such as A2D3. Representative cases are shown in Figure 1. To examine the quantitativeness of the SPK grading method, the correlation between the SPK grade and the corneal epithelial permeability to fluorescence, measured using an anterior fluorophotometer, was analyzed in 351 eyes diagnosed as having dry eye syndrome. Dry eye syndrome was diagnosed when a Schirmer I test was 5 mm or less or tear breakup time was 5 seconds or less. The magnitude of SPK in each eye was determined by one of us (K.M.). The corneal epithelial permeability to fluorescence was measured using a slitlamp fluorophotometer.

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First, autofluorescence intensity was measured at the central corneal stroma before instillation of fluorescein; the resulting value was considered as background fluorescence. Sodium fluorescein (3 µL) distilled to 0.5% in balanced salt solution with 0.46% oxyglutatione was instilled into the lower conjunctival sac using a micropipette. Ten minutes after instillation of the sodium fluorescein, the ocular surface was washed thoroughly with 20 mL of balanced salt solution with 0.46% oxyglutatione. Thirty minutes after the instillation of sodium fluorescein, the fluorescence intensity was measured at the central corneal stroma. The background value was subtracted from the average of 10 measurements. The values were converted to fluorescein concentration using a calibration line determined by a 0.50-mm-wide slide glass corneal model3,4 (low range: 
\[ y = 4.81 + 3.49x \] 
(high range: 
\[ y = -25.1 + 3.95x \] (where \( y \) is the fluorescein concentration [nanograms per milliliter], and \( x \) is the measurement count). The correlation between the SPK grade and fluorescein concentration was analyzed.

**RESULTS**

The grade distribution for 351 dry eyes is presented in the **Table**. No case was graded as A3D1. The average fluorescein concentration for each grade is shown in **Figure 2**. The higher the density and area grades were, the higher the fluorescein concentration, except for A3D2. The correlation between the sum of the area and density grades and the average fluorescein concentration in all cases is shown in **Figure 3**. There was a clear exponential correlation between the sum of the area and density grades and the fluorescein concentration in the cornea. The regression curve was 
\[ y = 61.2e^{0.59x} \] (where \( y \) is the fluorescein concentration [nanograms per milliliter] and \( x \) is the sum of area and density grades).

**COMMENT**

A grading method for SPK magnitude should be helpful in various situations, such as when performing multicenter evaluation of new drugs to treat corneal epithelial disorders or when describing the time course of changes in SPK magnitude. As far as we know, however, there has...
been no established method of grading SPK magnitude. Our method, based on slitlamp findings, establishes SPK area and density and hence facilitates a quantitative description of SPK. While the easy clinical application is an advantage of the method, the grading can be subjective and nonquantitative. In our previous study, 54 ophthalmologists were asked to grade 30 slides of eyes with or without SPK, using the grading method, and the distribution of the grades was analyzed. The highest percentage of agreement in area, density, and combination grades in each case ranged from 48.1% to 100%, from 48.1% to 100%, and from 31.5% to 100%, respectively. More than 50% of the ophthalmologists gave the same area, density, and combination grades for 29 (97%), 29 (97%), and 20 (67%) slides, respectively. In 6 of 10 cases, for which fewer than 50% of the ophthalmologists gave the same combination grade, the grades were mostly divided between 2 grades, and the percentages were greater than 70% when the 2 grades were combined. These results suggested the clinical usefulness of the SPK grading method. The distribution of the grades fell into a narrow range, however, and more than 50% of the ophthalmologists gave the same area and density grade for most of the cases. They judged the grades for 30 cases just after they were taught the definition of the grade. When the grading method is used routinely in clinical practice, the percentage of agreement should increase.

Several studies report that the anterior fluorophotometer quantitatively measures the degree of breakdown of corneal epithelial barrier function. 4-7 As shown in Figures 2 and 3, fluorescein concentration was related to both density and area grades of SPK. The higher the density and area grades, the higher the fluorescein concentration, except for A3D2 (Figure 2). This exception might have been due to the small number of cases with a grade of A3D2. The fluorescein concentration was measured at the central corneal stroma, and it might be that the fluorescein concentration depends on the density of SPK around the central cornea. The results indicated, however, that the area grade as well as the density grade affected the fluorescein concentration. One explanation is that the possibility of SPK around the central cornea increases as the area grade of SPK increases, and the average fluorescein concentration at the central corneal stroma in various eyes was correlated with the area grade of SPK as well as with the density grade.

Corneal epithelial disorders may indicate conditions that are more severe than SPK, such as corneal erosion, persistent epithelial defect, and filamentary keratitis. We did not include these more severe conditions, however, because the pathophysiologic mechanisms in these disorders are thought to differ from those in SPK. Our study demonstrates the clinical usefulness of the SPK grade, as it correlates positively with the corneal epithelial permeability to fluorescence.

Submitted for publication February 11, 2003; accepted June 17, 2003.

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Figure 2. The average fluorescein concentration measured with a slitlamp fluorophotometer. The higher the density and area grades, the higher the fluorescein concentration, except for A3D2.

**REFERENCES**