Atelocollagen Punctal Occlusion in Dry Eye Patients

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Purpose: To evaluate the efficacy and safety of atelocollagen punctal occlusion for dry eye patients.

Design: Prospective noncomparative interventional case series.

Methods: Atelocollagen was injected into the superior and inferior canaliculi of 52 eyes of 28 dry eye patients. Vital staining of the ocular surface, breakup time of tears (BUT), tear volume, and corneal epithelial permeability to fluorescein were examined before and 1, 2, 4, and 8 weeks after treatment.

Results: Rose bengal stain, fluorescein stain, BUT, and corneal epithelial permeability to fluorescence were significantly improved 1 week after atelocollagen punctal occlusion, and the improvement was maintained for up to 8 weeks after treatment.

Conclusions: Atelocollagen punctal occlusion effectively improves ocular surface disorders in dry eye patients.

Key Words: atelocollagen, dry eye, punctal plugs

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Although punctal plugs are effective for treating dry eye syndrome,[1–4] several problems have been reported, including frequent extrusion,[2–4] migration into the canaliculi,[5,6] infection,[6–8] and the discomfort of insertion. Atelocollagen is a collagen solution that is extracted from animal dermal tissue, from which antigenic telopeptides attached to both ends of the collagen molecule are eliminated by pepsin treatment.[9,10] Because atelocollagen is liquid when stored at 4°C to 10°C and forms a gel at room and body temperature,[9,10] it is clinically used to treat depressed scars or deformities caused by trauma or disease.[11–13] These characteristics might also be useful for the occlusion of ducts such as vessels[14] and lacrimal canaliculi[15,16] to treat diseases. In this study, the efficacy and safety of punctal occlusion with atelocollagen for treating dry eye syndrome were investigated.

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DESIGN

Prospective Noncomparative Interventional Case Series

Patients and Methods

Subjects were 52 eyes of 28 patients diagnosed with dry eye syndrome at the Miyata Eye Hospital. None of the patients had a history of ocular surgery. All patients gave informed consent before participation. The research protocol adhered to the tenets of the Declaration of Helsinki. The patients were 27 women (50 eyes) and 1 man (2 eyes). Eleven eyes of 6 patients with Sjogren syndrome were included. The age ranged from 27 to 78 years (mean ± SD, 58.0 ± 14.8 years).

Before atelocollagen punctal occlusion, the patients used eyedrops of 0.1% sodium hyaluronate (Santen Pharmaceuticals, Osaka, Japan) and/or preservative-free artificial tears (Santen Pharmaceuticals). After treatment, they used the same eyedrops as before treatment and were allowed to use these eyedrops as frequently as needed. The frequency of eyedrop usage was analyzed.

Atelocollagen used in this study was extracted from bovine epidermis, sterilized, and packed in a sterile tube by Koken (Tokyo, Japan). After patients lay down in a supine position, a 27-gauge blunt needle attached to a sterile tube containing 0.2% atelocollagen solution was inserted 2 to 3 mm into a punctum, and atelocollagen solution was injected into the canaliculi by pushing a plunger and slowly retracting a needle to fill a canaliculus with atelocollagen. When a canaliculus was full of atelocollagen, slightly opaque atelocollagen gel could be seen at the punctum. Both superior and inferior puncta were treated in each eye.

Slit-lamp microscopic examination was performed every week after the treatment to examine the presence and possible adverse effects of the atelocollagen punctal occlusion. Rose bengal stain, fluorescein stain, break up time of tears (BUT), tear volume, and corneal epithelial permeability to fluorescence were examined before and 1, 2, 4, and 8 weeks after treatment. Rose bengal staining was graded from 0 to 3 at the nasal conjunctiva, temporal conjunctiva, and cornea, and the sum of the 3 grades was considered as the score for each eye. Fluorescein staining in the cornea was scored using our earlier method,[17] which used area and density of the lesion as parameters. Briefly, the area and density of fluorescein staining in the cornea were graded from 0 to 3. Area grade was defined depending on the total sum of the affected area as follows: A0, there is no punctate staining; A1, the area occupies less than one-third of the cornea; A2, the area occupies one-third to two-thirds of the cornea; A3, the area occupies more than two-thirds of the cornea. Density grade was defined as follows: D0,

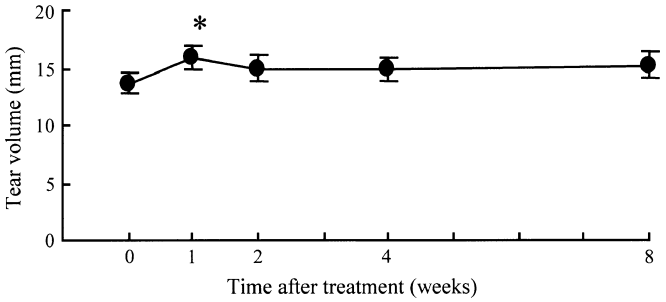

FIGURE 1. Mean (standard error) tear volume measured with the cotton thread test after atelocollagen punctal occlusion. Mean tear volume significantly increased at 1 week after treatment and slightly decreased thereafter. *$P < 0.05$.

there is no punctate staining; D1, the density is sparse; D2, the density is moderate; D3, the density is high and the lesions overlap one another. Grading was represented as a combination of the area and density grades, eg, A2D3. In the present study, the sum of the area and density grades was designated to be the score for each eye. BUT was measured using a stopwatch. Tear volume was measured using the phenol red cotton thread test. Corneal epithelial permeability to fluorescence was measured using a slit-lamp fluorophotometer (FL-500, Kowa, Tokyo) as described previously.[17,18] First, autofluorescence intensity was measured at the central corneal stroma, and the value was designated as the background fluorescence. Sodium fluorescein (3 μL; Alcon, Fort Worth, TX) distilled to 0.5% in BSS PLUS (Alcon) was instilled into the lower conjunctival sac with a micropipette, and the ocular surface was washed thoroughly with 20 mL of BSS PLUS 10 minutes after instillation. Thirty minutes after instillation, the fluorescence intensity at the central corneal stroma was measured. Values obtained were converted to fluorescein concentrations based on calibration curves obtained with a 0.5-mm-wide slide glass corneal model.[19,20]

Before and after the treatment, the patients were asked to score 6 ocular symptoms: fatigue, dryness, pain, itching, glare, and epiphora. The score ranged from 0 to 5, with higher scores indicating worse ocular status.

A paired *t* test or Wilcoxon rank sum test was used to compare pre- and posttreatment values at each examination. *P* values of less than 0.05 were considered statistically significant.

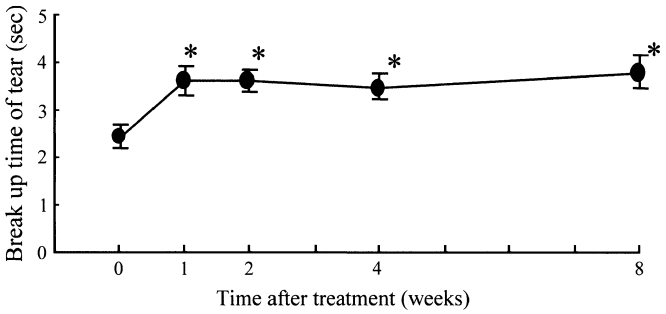

FIGURE 2. Mean (standard error) breakup time of tears after atelocollagen punctal occlusion. Mean breakup time of tears significantly increased after treatment. *$P < 0.0001$.

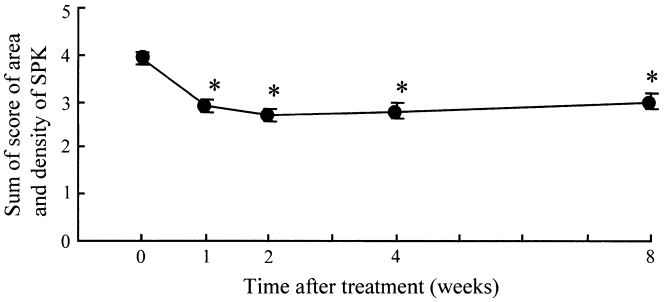

FIGURE 3. Average (standard error) of the sum of the area and density of superficial punctate keratopathy after atelocollagen punctal occlusion. The average of the sum of the area and density scores of superficial punctate keratopathy significantly decreased after treatment. *$P < 0.0001$.

RESULTS

The frequency of eyedrop use 8 weeks after treatment decreased in 31 eyes, increased in 4 eyes, and stayed the same in 9 eyes when compared with pretreatment frequency. In 8 eyes, the frequency of the use of 1 type of eyedrop was increased, and that of another type of eyedrop was decreased. Out of these 8 eyes, 6 eyes saw increased use of 0.1% sodium hyaluronate eyedrop and decreased use of preservative-free artificial tears, and 2 eyes saw the opposite.

Before treatment, mean tear volume measured with the cotton thread test was 13.7 mm. Mean tear volumes significantly increased at 1 week after treatment ($P = 0.029$) and slightly decreased thereafter (Fig. 1).

Mean BUT was 2.4 seconds before treatment. Mean BUT increased after treatment (Fig. 2), and all posttreatment values were significantly higher than pretreatment values ($P < 0.0001$).

The average of the sum of the area and density score of superficial punctuate keratopathy was 3.9 before treatment and decreased after treatment (Fig. 3). All posttreatment values were significantly smaller than pretreatment values ($P < 0.0001$).

Average rose bengal staining score was 5.8 before treatment and decreased after treatment (Fig. 4). All posttreatment values were significantly smaller than pretreatment values ($P < 0.0001$).

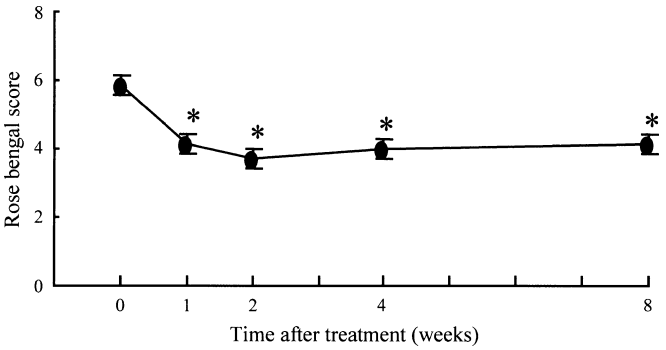

FIGURE 4. Mean (standard error) rose bengal score after atelocollagen punctal occlusion. Mean rose bengal score significantly decreased after treatment. *$P < 0.0001$.

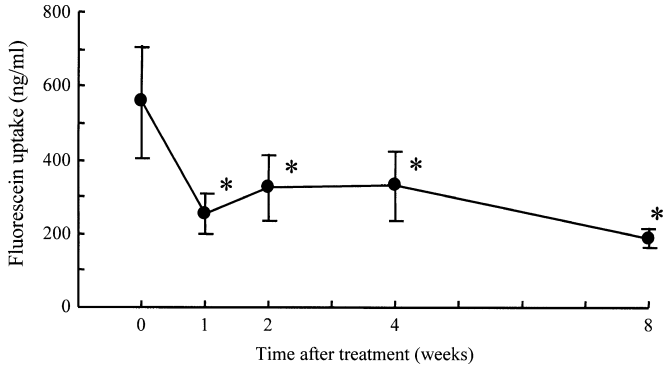

FIGURE 5. Mean (standard error) fluorescein uptake measured using a slit-lamp fluorophotometer after atelocollagen punctal occlusion. Mean fluorescein uptake significantly decreased after treatment. *$P < 0.01$.

Average fluorescein uptake was 558 ng/mL before treatment and decreased after treatment (Fig. 5). Average fluorescein uptake after treatment was significantly lower than pretreatment values (1 week, $P = 0.0036$; 2 week, $P = 0.0015$; 4 week, $P = 0.0053$; 8 week, $P = 0.0049$).

The scores of ocular symptoms before and after the treatment are shown in Figure 6A–F. Ocular fatigues, dryness, pain, and glare improved after treatment while ocular itching and epiphora remained at pretreatment levels.

DISCUSSION

In the present study, rose bengal stain, fluorescein stain, BUT, and corneal epithelial permeability to fluorescence were significantly improved at 1 week after atelocollagen punctal occlusion, and the improvement was maintained for up to 8 weeks after treatment. In addition, the frequency of eyedrop use for treatment of dry eye decreased in most patients. Moreover, such ocular symptoms as fatigue, dryness, pain, and glare improved after treatment, and the improvement was also maintained for up to 8 weeks after treatment. These results suggest that atelocollagen punctal occlusion is effective for treating ocular surface disorders in patients with dry eye. Although tear volume slightly increased 1 week after treatment, the increase was not statistically significant. The cotton thread test might not be sensitive enough to detect an increase in tear volume after treatment. But even if the increase in tear volume was not significant, instilled eyedrops might remain on the ocular surface for a longer period because of the punctal occlusion, thereby ameliorating ocular surface disorders. Ocular symptoms improved after punctal occlusion probably because punctal occlusion lowers tear film osmolarity.[21]

Atelocollagen punctal occlusion has a couple of possible advantages over the use of a silicone punctal plug. First, injection of atelocollagen is easier to perform than that of silicone and causes less discomfort to patients. Thus, patients might be more tolerant to the treatment when repetitive

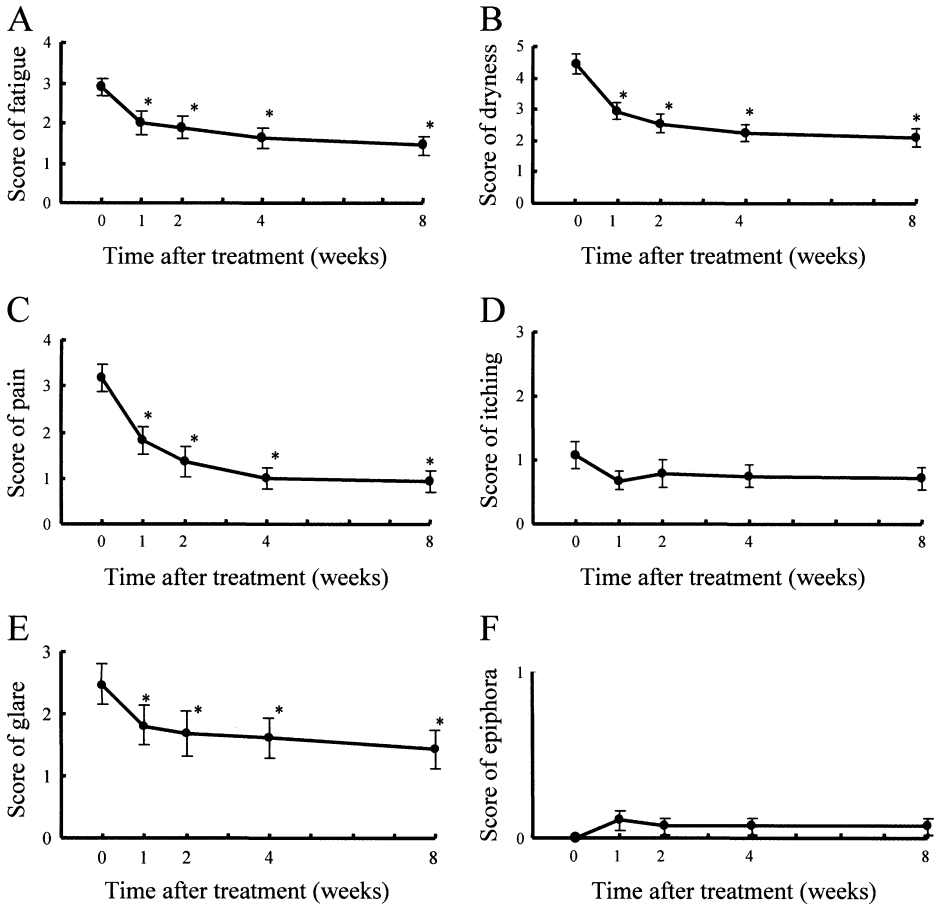

FIGURE 6. Mean (standard error) score of ocular symptoms after atelocollagen punctal occlusion. Ocular fatigue, dryness, pain, and glare improved after treatment, whereas ocular itching and epiphora remained at pretreatment levels. *$P < 0.0001$.

treatments are needed. Second, because atelocollagen is liquid and forms a gel when injected into the canaliculi, prior size determination is not necessary, and the injected atelocollagen is likely to occlude the punctum more firmly than silicone plugs. On the other hand, whereas silicone punctal plugs can be easily removed when patients complain of epiphora, atelocollagen punctal occlusion cannot be removed in such cases. This can be a major disadvantage of atelocollagen punctal occlusion.

Atelocollagen has been clinically used to treat depressed scars or deformities caused by trauma or disease.[11–13] In those studies, repetitive injections of atelocollagen were necessary to maintain the effect of the injection, indicating that injected atelocollagen is gradually adsorbed in vivo. Although the length of retention of atelocollagen punctal occlusion could not be examined, the results of the present study indicated that improvement of ocular surface disorders was maintained for up to 8 weeks after treatment. Further studies are necessary to examine how long injected atelocollagen continues to occlude canaliculi and how long the ocular surface improvement is maintained.

Because atelocollagen is extracted from bovine epidermis, transspecies infection of pathogens, especially prions, is a big concern. Atelocollagen used in the present study was extracted from cows harvested in the United States when no cows with bovine spongiform encephalopathy had been reported in the United States, suggesting no prion infection of atelocollagen used in this study. Alternative animals or alternative sources of collagen should be explored, however, to exclude infectious pathogens from material for clinical use.

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