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Thermokeratoplasty as a Treatment for Ulcerative Keratitis Caused by Corneal Endothelial Degeneration in Two Dogs

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Abstract : A 13-year-old, female, Shih-tzu and a 10-year-old, female, Yorkshire terrier were presented with ulcerative keratitis caused by corneal endothelial degeneration. Generalized corneal edema, conjunctival hyperemia, focal corneal pigmentation, corneal neovascularization, sub-epithelial bullae, and positive fluorescein staining were observed during ophthalmic examinations. Thermokeratoplasty was performed on the overall edematous corneas. Healing of the cornea was completed within 25 days and corneal ulceration has not recurred after healing of the cornea in both cases. Other ocular complications were not observed except for a slight increase in corneal pigmentation. According to this study, thermokeratoplasty could be an effective treatment for corneal ulceration secondary to corneal endothelial diseases in dogs.

Key words **:** corneal ulcer, endothelial degeneration, thermokeratoplasty, dog.

Introduction

Corneal endothelial degeneration is a progressive and vision-threatening ocular disease resulting from dystrophy of corneal endothelial cells and prevalent in old dogs. Corneal edema is a distinctive clinical sign, and focal edema around the limbus gradually progresses to the entire cornea. Middle-aged dogs of certain breeds such as Boston Terriers, Chihuahuas, and Dachshunds often experience the same corneal endothelial disease, and this refers to corneal endothelial dystrophy (10).

Corneal endothelial cells are typically hexagonal in shape and arranged in a mosaic pattern in a single layer. The endothelial cell density is approximately over 2600 cells/mm^2 in normal young dogs (< 1 year of age). The density gradually decreases with aging, resulting in an increase in the cell size and a loss of the typical hexagonal shape (11). If the endothelial cell density falls to below 500~800 cells/mm^2, corneal decompensation can develop. As a result, a typical clinical sign, corneal edema appears (17). On ophthalmic examination, the transparent cornea takes on a bluish white appearance with or without conjunctival hyperemia. Corneal edema initially starts in the temporal area around the limbus and gradually progresses to the entire cornea over several months to a few years. However, corneal neovascularization is not a common clinical sign in corneal endothelial degeneration. Contralateral eyes sometimes show no clinical signs upon initial presentation; however, this can progress to bilateral disease. On slit-lamp biomicroscopic examination, the corneal thickness is increased, and intra-, sub-epithelial bullae and sub-epithelial scaring are observed (10). A corneal ulcer or erosion is often induced by a spontaneous rupture of the intra- and sub-epithelial bullae (15).

Several medical and surgical treatments can be applied to corneal endothelial degeneration. As a medical treatment, topical hyperosmotic agents such as 5% NaCl are used to reduce corneal edema (12) and topical broad spectrum antibiotics are also employed to prevent secondary bacterial infections. Surgical options include penetrating keratoplasty, thermokeratoplasty (10) and, recently, keratoleptynsis (16). Among them, penetrating keratoplasty can be a definitive treatment because a damaged cornea can be substituted with a healthy one. However, this treatment has some limitations such as immune rejection, a high cost, and a difficult post-operative care regimen. Therefore, penetrating keratoplasty is not commonly performed in veterinary medicine (7). Keratoleptynsis can be applied to cease the progression of corneal edema in early stages. When the size of the corneal edema is less than 5 mm, the epithelia of the edematous cornea are removed with debridement, and this is followed by the covering of the de-epithelialized area with a thin conjunctival flap (16).

For the thermokeratoplasty, heat can be applied onto the cornea using a cautery device, a laser, or via microwaves. Contraction of the collagen fiber is induced by intentional heat application to the corneal stroma, leading to the formation of a sub-epithelial scar (5,14,18). The sub-epithelial scar tissue is a fibrous barrier that suppresses the formation of intra- and sub-

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epithelial bullae. As a result, any additional corneal ulcers or erosions can be reduced (15). Therefore, we reported the outcomes, prognosis and complications related to thermokeratoplasty in the treatment of a corneal ulcer induced by corneal endothelial degeneration in 2 dogs.

Cases

Case 1

A 13-year old, female, Shih-tzu was presented for bilateral corneal edema. On an ophthalmic examination, conjunctival hyperemia, corneal edema, corneal pigmentation, and intra- and sub-epithelial bullae were observed in both eyes. Corneal neovascularization was shown and fluorescein staining was also positive in the left eye (Fig 1A-1). Ulcerative keratitis caused by corneal endothelial degeneration in the left eye was diagnosed because the cornea was shown typical lesions (corneal edema with sub- and intra-epithelial bullae) and positive fluorescein staining. To reduce the symptoms of corneal edema, 5% NaCl (4 times/day) was applied to both eyes and tobramycin (OcuRacin®, Samil, Korea, 4 times/day) was also dropped to control a secondary bacterial infection in the left eye. In addition, autologous serum (4 times/ day), and 0.5% carboxymethylcellulose sodium (Refresh Plus™, Allergan, USA, pro re nata) were also prescribed to facilitate the epithelial growth and to palliate the symptoms in the left eye, respectively.

Thermokeratoplasty was performed for the left eye under inhalant anesthesia. The adnexa, cornea and conjunctiva were flushed with 0.2% povidone iodine and Hartmann's solution to sterilize the surgical fields. After an eye speculum was placed to expose the entire cornea, the loose corneal epithelium was removed from the underlying cornea using sterile cotton-tipped applicators. A sterile handheld cautery unit with a low-temp microfine tip (Bovie®, Bovie Medical, USA) was used to apply heat to the cornea. The application of heat was performed on the entire cornea in a circular pattern at 2 mm intervals from the central cornea to the peripheral. To apply the proper amount of heat, the tip of the cautery unit was activated by pushing the button until the tip became red in color. The tip was then inactivated by releasing the button. When the tip color was no longer red, the tip was placed into contact with the cornea until a stromal contraction appeared. It was then immediately removed from the cornea (Fig 2). After the heat application, we carefully examined the cornea to identify signs of excessive heating, such as corneal burning or melting. Tobramycin (4 times/day), 5% NaCl (4 times/day), autologous serum (4 times/ day), atropine (OcuTropine®, Samil, Korea, 3 times/day for 3 days), and 0.5% carboxymethylcellulose sodium (pro re nata) were applied to the left eye. On the 25th day following thermokeratoplasty, the corneal ulcer had completely disappeared, and a combination eye drop consisting of dexamethasone, polymycin B and neomycin (Maxitrol®, Alcon Inc., Belgium) was instilled for 3 months to inhibit excessive corneal neovascularization, pigmentation and scarring. Subsequently, the eye drops were tapered; only 5% NaCl (3 times/day) was applied for 10 months after thermokeratoplasty.

No corneal ulcer or erosion was noticed up to 15 months after thermokeratoplasty. The only complication was a slight progression of corneal pigmentation, which was of little clinical importance (Fig 1A-2).

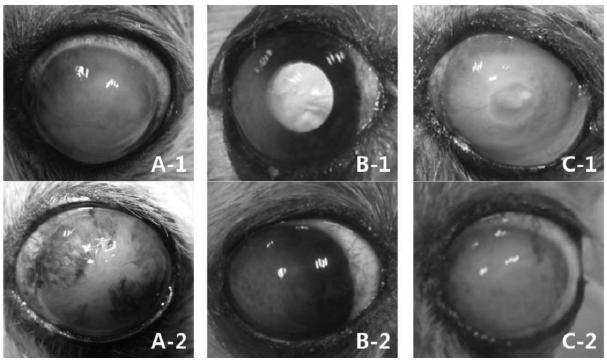

Fig 1. Clinical appearances and postoperative figures (A-1, A-2: left eye of case 1; B-1, B-2: right eye of case 2; C-1, C-2: left eye of case 2; A-1, B-1, C-1: before thermokeratoplasty; A-2: 9 months after thermokeratoplasty; B-2, C-2: 3 months after thermokeratoplasty). A-1: Diffuse corneal edema and corneal pigmentation around the medial limbus are shown. Fluorescein staining was positive in the superior-lateral quadrant. A-2: The cornea was healed and stabilized after thermokeratoplasty. Progression of corneal pigmentation is shown compared to A-1. B-1: Partial corneal edema at lateral limbus to pericentral cornea was observed. B-2: Progression of corneal edema was identified after thermokeratoplasty compared to B-1. C-1: Generalized corneal edema and corneal neovascularization are shown. Fluorescein staining was positive in the central cornea. C-2: The cornea was healed and stabilized with a slight increase in corneal pigmentation.

Case 2

A 10-year old, female, Yorkshire terrier was presented with a corneal ulcer in the left eye. The dog has been diagnosed

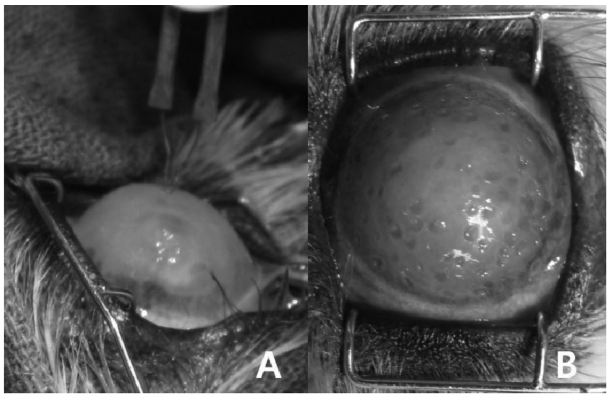

Fig 2. Intraoperative photographs of thermokeratoplasty (case 1). A: The tips of the cautery gently touch the cornea. B: The appearance of the cornea immediately after thermokeratoplasty show corneal stromal contracture around the heat-application site without corneal melting or burning.

with corneal endothelial degeneration at the age of 6 years. On an ophthalmic examination, generalized corneal edema was identified in the left eye, and focal edema (lateral limbus to mid central cornea) was observed in the right eye. Conjunctival hyperemia was shown in both eyes, with the left eye more severe than the right. Corneal neovascularization, corneal pigmentation, aqueous flare and hypopyon were observed in the left eye. Fluorescein staining was positive in the left central cornea (Figs 1B-1, C-1). Ulcerative keratitis caused by corneal endothelial degeneration in the left eye was diagnosed because the cornea was shown typical lesions (corneal edema with sub- and intra-epithelial bullae) and positive fluorescein staining. 5% NaCl (4 times/day) was applied to both eyes to palliate the corneal edema. Levofloxacin (Cravit®, Santen Pharmaceutical Co., Japan, 8 times/day), autologous serum (8 times/day), 5% acethylcysteine (4 times/day), 1% EDTA (4 times/day) and 0.5% carboxymethylcellulose sodium (pro re nata) were instilled in the left eye.

Thermokeratoplasty was performed on the entire cornea of the left eye and the edematous corneal region of the right eye. The procedure was identical to that of case 1 except for applying of temporary partial tarsorrhaphy for 11 days after thermokeratoplasty to protect the cornea and promote ulcer healing. Levofloxacin (4 times/day), 5% NaCl (4 times/day), autologous serum (4 times/day), 1% EDTA (3 times/day), atropine (3 times/day for 3 days) and 0.5% carboxymethylcellulose sodium (pro re nata) were prescribed for both eyes. The eye drops were gradually tapered and no eye drops were needed 3 months after surgery.

No sign of corneal ulcers appeared 11 days after thermokeratoplasty. Maxitrol® was applied for 1 month to inhibit excessive corneal neovascularization, pigmentation and scarring. Corneal edema of the right eye was progress to the central cornea 5 months after thermokeratoplasty. However, there was no recurrence of corneal ulcer up to 10 months after surgery and the slight progression of corneal pigmentation was the only non-clinically significant complication (Figs 1B-2, C-2).

Discussions

Recurrent or persistent corneal ulcer is common in patients with corneal endothelial degeneration as a consequence of intra- and sub-epithelial bullae. During the same period as the thermokeratoplasty cases in this study, 2 dogs presented with corneal ulcer secondary to corneal endothelial degeneration at the Veterinary Medical Teaching Hospital of Seoul National University. They did not undergo thermokeratoplasty because the owner rejected general anesthesia. In these cases, they had only medical therapy with debridement of the loose epithelium and grid keratotomy. One case progressed to a persistent ulcer after more than 1 month and the other had two instances of recurrence for 3 months. However, no recurrence or persistent ulcers were observed in thermokeratoplasty cases. Therefore, it appears that corneal ulcers induced by corneal endothelial degeneration could be successfully treated with thermokeratoplasty rather than medical therapy with grid keratotomy.

Corneal endothelium involves active pump mechanisms which play an essential role in maintaining corneal transparency and mechanical strength (10). Therefore, dysfunction of the corneal endothelium leads to excessive stromal hydration. In cases involving corneal endothelial degeneration, intra- and sub-epithelial bullae typically form due to excessive fluid influx to the corneal stroma, and the bullae spontaneously ruptur if the corneal epithelium cannot resist the hydraulic power induced by the fluid influx. After the rupture of the bullae, corneal erosion or ulcers are formed. This type of ulcer often progresses to a persistent or recurrence ulcer. In cases of severe corneal edema induced by corneal ulcer secondary to corneal endothelial degeneration, this refer to bullous keratopathy (15).

Several medical and surgical treatments can be applied to treat corneal endothelial dystrophy. Because hyperosmotic agents can inhibit intra- and sub-epithelial bullae formation, they can be useful for corneal ulcers secondary to corneal endothelial degeneration. However, this agent has little effect on stromal hydration (12).

Surgical treatments for corneal endothelial degeneration include penetrating keratoplasty, keratoleptynsis and thermokeratoplasty. Although penetrating keratoplasty is a definitive treatment for corneal endothelial degeneration, corneal neovascularization is a risk factor for graft rejection (4). In addition, dogs have a higher rejection rate than humans and surgical techniques for animal species are not well established (7). Also, there were no adequate eyes for keratoleptynsis in our cases because the sizes of corneal edema exceeded 5 mm.

Thermokeratoplasty was first introduced to treat hyperopia in humans and a thermokeratophore was used to apply heat to the cornea early (1,3,18). Subsequently, this surgical technique was widely used to correct hyperopia in humans and laser or microwave energy was used to transfer the heat energy precisely to the cornea (5,8). In veterinary medicine, thermokeratoplasty was mainly used for corneal ulcers secondary to corneal endothelial degeneration and spontaneous chronic corneal epithelial defects (6,15).

The corneal epithelium and basement membrane are dissolved, and the collagen fibers shrink to about 1/3 of their normal length when heat in the range of 90~130°C, is applied to the cornea (18,20). After thermokeratoplasty, sub-epithelial scar tissue is formed serving a barrier function against the corneal uptake of fluid. The formations of intra- and sub-epithelial bullae are reduced and instances of corneal erosion or ulcer are also decreased (15). Corneal transparency is improved and vision is improved as well because the influx of fluid to the corneal stroma is reduced. Although there are few methods to evaluate the vision improvement in animals, the areas to which heat was applied, were more transparent than before thermokeratoplasty in our cases.

The tip temperature of the cautery used in our report reaches 343°C after 4 minutes of activation. The temperature cannot be precisely controlled by the activation button (15). However, as mentioned above, the temperature range is sufficiently wide

(90~130°C), and we did not observe any signs of over-heating such as corneal melting and burning when the tip color returned to normal. Thermokeratoplasty should be performed in conjunction with careful observance of the cornea to avoid excessive heat conduction.

Regeneration of anterior corneal structures after thermokeratoplasty can differ depending on the species. In rhesus monkeys, corneal epithelium is regenerated less than 1 month after experimental thermokeratoplasty, and regeneration of the basement membrane requires approximately 6 weeks (3,13). Re-epithelialization is complete after less than 1 week in rabbits and, in human the epitheliums are regenerated approximately 1 month after keratoplasty similar to those of rhesus monkeys (18). In humans, regeneration of the corneal epithelium is delayed in some cases on account of the abnormal regeneration of the basement membrane and Bowman's membrane (9). The healing times for a corneal ulcer after debridement only, debridement and grid keratotomy, and thermokeratoplasty are 23.4 days, 13.4 days, and 2.1 weeks in dogs, respectively (6,19). In the aforementioned previous report, thermokeratoplasty did not delay corneal healing in dogs. Similarly, in our report, the healing times after thermokeratoplasty were 25 days and 11 days in case 1 and case 2, respectively.

Reported complications of thermokeratoplasty are retardation of re-epithelialization, necrosis of the corneal stroma, iritis with hypopyon and corneal neovascularization in humans (2,9). In dogs, 2 of 13 cases showed corneal neovascularization after thermokeratoplasty (15). In our cases, progression of corneal pigmentation was noted. One considerable factor to explain this complication was corneal neovascularization before thermokeratoplasty.

Conclusions

Corneal ulceration due to corneal endothelial degeneration is easily recurrent in spite of intensive medical treatment and surgical approach, leading to chronic deep corneal ulceration and uveitis. In this report, the thermokeratoplasty dissolved the corneal ulceration due to corneal endothelial degeneration in 2 eyes. The results indicated that thermokeratoplsty could be an effective treatment for corneal ulcers secondary to corneal endothelial degeneration.

Acknowledgements

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개의 각막내피세포 변성증에 의한 각막 궤양에 적용한 각막열성형술 2례

박영우 · 김세은 · 안재상 · 안정택 · 이예스란 · 이의리 · 이나영* · 서강문 · 정만복[1]

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요 약 : 13살 암컷 시츄 (증례 1) 와 10살 암컷 요크셔테리어 (증례 2) 가 각막 내피세포 변성증에 의한 각막궤양으로 내원하였다. 안검사 상에서 증례 2의 우안은 각막 외측에 국소적인 각막 부종이 확인되었고, 나머지 3 안에서는 전체 각막에서 부종이 확인되었다. 두 증례 모두 좌안에서 결막 충혈, 국소적인 각막 색소 침착, 각막 신생혈관화, 상피하수포가 관찰되었고, 형광 염색 시 양성 반응이 확인되었다. 각막열성형술은 증례 1 에서, 좌안의 전체 각막에, 증례 2에서, 좌안의 전체 각막과 우안의 각막부종 부위에 실시하였다. 증례 2 에서, 술 후 각막 치유를 촉진시키기 위해 일시적으로 양안 안검 봉합을 실시하여, 11일간 유지하였다. 각막 궤양은 증례 1 에서, 25일째, 증례 2 에서, 11 일째 완전히 치유되었다. 증례 1은 술 후 15 개월, 증례 2는 술 후 10 개월간 각각 각막궤양이 재발되지 않았다. 각막 색소 침착이 수술 전보다 진행되었으나, 그 외 임상적으로 중요한 부작용은 관찰되지 않았다. 각막 내피세포 변성증에 의한 궤양의 경우, 지속성 또는 재발성 양상으로 진행하여 심층 각막궤양 및 포도막염과 같은 속발증이 병발하는 경우가 많다. 그러므로, 본 증례에서 보고한 바와 같이 각막열성형술은 각막내피세포변성증에 의한 각막궤양에 효과적인 치료법으로 생각된다.

주요어 : 각막 궤양, 각막 내피세포 변성증, 각막열성형술, 개