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Nontraumatic Corneal Perforation

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Purpose. To study the predisposing conditions, treatments, and visual outcomes of nontraumatic corneal perforations. **Methods.** A retrospective chart review was conducted of all nontraumatic corneal perforations seen between January 1992 and December 1998, with ≥3 months of follow-up, at the Cornea Service Wills Eye Hospital. **Results.** A total of 40 nontraumatic corneal perforations was analyzed. Sixty-two percent of the cases were female. At presentation, 35 of 40 eyes (87.5%) had best corrected visual acuity of 20/200 or worse. The most common diseases associated with perforations were keratoconjunctivitis sicca (12 eyes, 30%), bacterial keratitis (6 eyes, 15%), exposure keratopathy (5 eyes, 12.5%), and herpes simplex virus (HSV) keratitis (4 eyes, 10%). Visual acuity improved ≥2 Snellen lines in 3 of 8 eyes (37.5%) treated with penetrating keratoplasty, 5 of 14 eyes (35.7%) treated with tissue adhesive, and 1 of 12 eyes (8.3%) given medical treatment. After allowing for the different levels of presenting vision, treatment modality was not significantly related to final visual outcome. **Conclusion.** Keratoconjunctivitis sicca is the most common underlying disease associated with nontraumatic corneal perforation. Corneal perforations were managed successfully using tissue adhesive, medical therapy, or penetrating keratoplasty. Treatment depended on the characteristics of the perforation and on the visual potential of the eye.
Key Words: Corneal perforation—Tissue adhesive—Penetrating keratoplasty.

Nontraumatic corneal ulceration leading to perforation is the result of many different noninfectious and infectious destructive conditions of the cornea. Because corneal perforation has a high ocular morbidity, prompt recognition and treatment may preserve useful vision.[1] Failure to diagnose and treat a perforation early can lead to further corneal damage, cataract formation, glaucoma development, endophthalmitis, and loss of the eye. Available treatments for the management of nontraumatic corneal perforation include medical treatment,[2,3] tissue adhesive,[4,5] lamellar keratoplasty, and penetrating keratoplasty (PK).[1,3,6]

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PATIENTS AND METHODS

The records of patients with the diagnosis of corneal perforation without a history of eye trauma or corneal surgery who were treated on the Cornea Service at the Wills Eye Hospital from February 1992 through January 1999 with at least three months follow-up, were reviewed retrospectively. If the patients had repeated episodes of corneal perforations in the same eye, only the first corneal perforation was analyzed. Diagnoses were based on clinical history, biomicroscopic examination, tear-film studies, as well as smears and cultures.

The data analyzed included patient age, sex, best corrected visual acuity (BCVA) at presentation, final BCVA, size, location and shape of corneal perforation, ocular history, and medical treatment. Treatment and visual outcome also were analyzed. Visual outcomes as they related to varying diagnoses were analyzed by examining the covariance of final visual acuity as the dependent variable and the baseline visual acuity as the covariate, with treatment as the grouping variable. The Wilcoxon rank sum test for independent groups was used to analyze the correlation between age and rheumatoid arthritis (RA).

Histoacryl (B. Braun Melsungen AG D-34209, Melsungen, Germany) was used as a tissue adhesive. It was applied under topical proparacaine anesthesia after the insertion of a lid speculum. The surrounding epithelium was scraped, and the area of the perforation was dried with a cellulose sponge. A small amount of tissue adhesive was applied to the perforation and ulcer, reaching the surrounding normal basement membrane tissue. A flat, low-water-content bandage soft contact lens was placed before removal of the lid speculum.

In this study, we treated corneal perforations with tissue adhesive when the perforations were <1.0 mm in diameter at the level of Descemet's membrane and were concave. If active infection was present, it was treated for 48–72 hours before tissue adhesive was applied. We managed corneal perforations medically when they were small (≤1.0 mm in diameter), without iris prolapse, and could not be treated with tissue adhesive because of ectatic configuration, or when associated with a poor visual prognosis for PK. Medical treatments used to manage perforations included patching and/or shielding, topical and systemic hypotensive agents to diminish the flow of aqueous humor, topical and systemic antibiotics (all received topical and systemic antibiotics), and antifungal agents (in cases of fungal keratitis).

A PK was used to treat large corneal perforations (>1.0 mm in diameter) with iris prolapse, with a flat or very shallow anterior chambers for >48 hours, and with good visual potential that failed to respond to medical treatment or tissue adhesive. The corneal button was removed, and a 0.5 mm oversized donor cornea was

TABLE 1. *Nontraumatic corneal perforation*

No.	Age (yr)	Sex	Presentation BCVA	Diagnosis	History	Final BCVA
1	69	F	20/200	KCS/RA		20/25
2	65	F	CF 2′	Sterile corneal ulcer	Corneal ulcer 3 wk; hypothyroid	20/40
3	74	F	LP	KCS		LP
4	82	M	20/200	OCP	Corneal ulcer 4 wk	20/100
5	82	F	HM	*S. aureus* corneal ulcer	HZO 4 mo	20/200
6	65	F	20/200	KCS/Sjögren's syndrome	Epith. defect 1 mo	20/30
7	38	M	20/200	HSV keratitis	Recurrent HSV keratitis 12 yr	20/200
8	39	F	HM	HSV keratitis	HSV keratitis 7 yr	HM
9	73	F	HM	*Pseudomonas + S. aureus* corneal ulcer	Corneal ulcer 3 wk, HZO 9 yr + recurrent trichiasis	HM
10	85	F	LP	*S. aureus* corneal ulcer	HZO 1 yr	LP
11	45	F	20/40	Rosacea	Seasonal allergy	20/30
12a	73	F	HM	KCS/Sjögren's syndrome	RA	CF
12b			HM			HM
13	91	M	CF 1′	Entropion		HM
14a	74	F	20/200	KCS		20/400
14b			20/80			CF 3′
15a	71	M	20/80	KCS/Sjögren's syndrome	RA, blepharitis	20/80
15b			CF 3′			20/70
16	41	M	20/400	Rosacea		20/60
17	54	F	HM	Fungal (filament, Alterania species) corneal ulcer	HZO 6 yr, neurotrophic keratopathy	LP
18	75	M	LP	Exposure keratopathy	Ptosis repair, NVG, hypothyroid	NPL
19	25	F		Corneal ulcer (neg. culture)	Down syndrome, hypothyroid	
20	55	F	HM	Exposure keratopathy/neuroparalysis keratopathy	CVA, facial palsy	NLP
21	49	M	CF 1′	Exposure + neuroparalysis keratopathy	Radiation for maxillary sinus adenocarcinoma	CF 1′
22	73	M	HM	KCS/Sjögren's syndrome		CF 6′
23	66	F	20/200	Exposure keratopathy	Thyroidectomy	20/400
24	55	F	20/60	Chronic staph, hypersensitivity	Hypothyroid	20/400
25	36	F	CF	Corneal ulcer (neg. culture)	NIDDM, ulcerative colitis	NLP
26	58	M	20/400	Coag. neg. *Staphylococcus + S. viridans* corneal ulcer	Rosacea, eczema, atopic dis.	20/80
27	87	F	HM	OCP		NLP
28	41	M	CF 1′	HSV keratitis	Recurrent HSV keratitis 20 yr	20/200
29	49	F	20/60	KCS/Sjögren's syndrome	RA	20/60
30	77	M	HM	Exposure kertopathy	Lid surgery or skin cancer	NLP
31	79	M	LP	HZO	Temporal arteritis 8 mo	LP
32	42	F	HM	Fungal (candida) corneal ulcer	Corneal ulcer 3 wk, eczema	LP
33	76	F	LP	Fungal (filament *Chrysonilia* species) corneal ulcer	HZO, viral hepatitis carrier	LP
34	61	M	CF 2′	HSV keratitis	Recurrent keratouveitis, cirrhosis, lymphadenopathy	20/30
35	76	F	CF 4′	KCS		20/200
36	68	M	HM	*S. epidermidis + S. viridans* corneal ulcer	HZO 7 yr	HM
37	77	F	NLP	*S. viridans* corneal ulcer	Lid surgery 1 yr/blepharitis	NLP

sutured using a 10-0 nylon interrupted suture technique, after peripheral iridectomies were performed. Occasionally, a lamellar keratoplasty was performed using full-thickness corneal donor tissue but leaving some host tissue peripheral to the perforation in the recipient bed. We avoided conjunctival flaps in patients with corneal perforations. Generally, the size of the perforation and visual potential, but not the location (peripheral vs. central), determined the management.

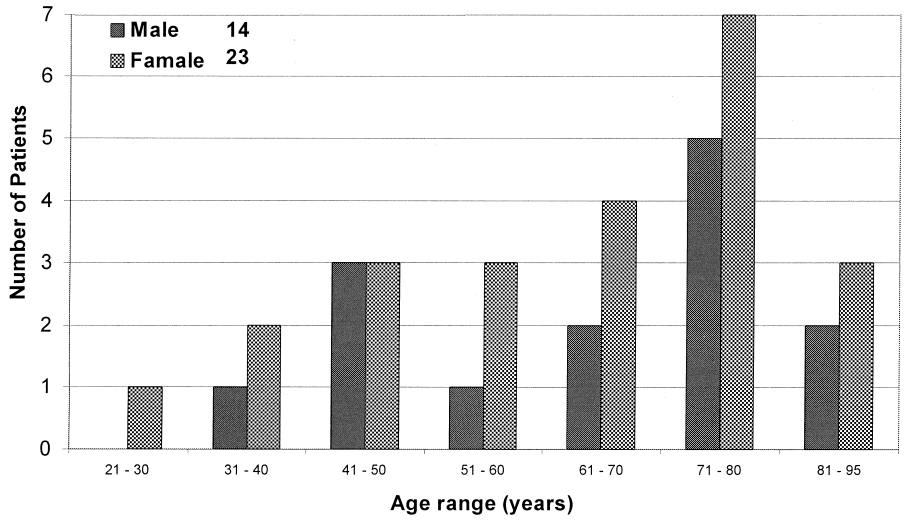

FIG. 1. Age and sex distribution of patients.

TABLE 2. *Initial and final best corrected visual acuity*

Visual acuity	Initial (eyes)	Final (eyes)
20/20–20/40	1	5
20/50–20/100	4	6
20/200–20/400	8	7
Count fingers	8	4
Hand motion	12	5
Light perception	5	6
No light perception	1	6
Not recorded	1	1

TABLE 3. *Causes of nontraumatic corneal perforation*

Diagnosis	Male	Female	Total
KCS	2	7	9
Bacterial keratitis	2	4	6
Exposure keratopathy	3	2	5
HSV keratopathy	3	1	4
Fungal keratitis	0	3	3
OCP	1	1	2
Rosacea	1	1	2
HXV keratopathy	1	0	1
Entropion	1	0	1
Chronic *staphylococcal* hypersensitivity	0	1	1
Corneal ulcer (unknown cause)	0	3	3

KCS, keratoconjunctivitis sicca; HSV, herpes simples virus; OCP, ocular cicatricial pemphigoid; HZV, herpes zoster virus.

TABLE 4. *Organisms isolated on culture*

Organism	Number
Bacteria	
Staphylococcus aureus	3
Streptococcus viridans	3
Staph. coagulase negative	2
Pseudomonas	1
Fungus	
Filamentous fungi	2
Candida	1

RESULTS

A total of 40 eyes of 37 patients were treated for nontraumatic corneal perforations over a seven-year period (Table 1). There were 14 men (38%) and 23 women (62%). The ages ranged from 25 to 91 years, with a mean of 63.4 years (Fig. 1). The follow-up period ranged from 3 to 84 months (mean, 24.5 months).

At presentation, 35 eyes (87.5%) had a BCVA of ≤20/200 (Table 2). One patient had Down's syndrome, and visual acuity could not be tested accurately. The location of the perforation was central in 22 eyes and peripheral in 18 eyes.

The most common cause of perforation was keratoconjunctivitis sicca (KCS) in 12 eyes of nine patients. Other causes included bacterial keratitis (six eyes), exposure keratopathy (five eyes), HSV keratitis (four eyes), fungal keratitis (three eyes), ocular pemphigoid (two eyes), and rosacea (two eyes) (Table 3). Cultures or scrapings (Table 4) confirmed the presence of bacterial or fungal infections.

The underlying medical diseases included secondary Sjögren's syndrome related to RA (five patients), thyroid disease (two patients with exposure keratopathy and three on thyroid medication only), and rosacea (three patients), as well as primary Sjögren's Syndrome (one patient). Nine perforations were secondary to infection (six bacterial and three fungal). Bacterial isolates included Staphylococcus, Streptococcus, and Pseudomonas. Fungal isolates included both yeasts and filamentous organisms (Table 4). There was no statistically significant correlation between age and RA (Wilcoxon rank sum test for independent groups, $p = 0.45$). Furthermore, we found no significant relationship between the average visual improvement in perforations associated with RA versus those related to another diagnosis after adjustment for different treatment modalities.

Tissue adhesive was applied in 15 eyes. Of the 15 eyes treated with tissue adhesive, 8 had to be reglued for recurrent leaks or glue dislodgment within several days and 1 eventually needed PK for refractory leaking. Thirteen eyes were treated by medical treatment. The wound sealing time for medically treated leaks ranged

TABLE 5. *Final best corrected visual gain or loss*

Diagnosis	Treatment	No. (eye)	Gain ≥2	Gain 1	0	Loss 1	Loss ≥2	NLP
KCS	Medical	2		1	1			
	Tissue adhesive	9	4	1	2	1	1	
	Tissue adhesive → PK	1			1			
OCP	Medical	2		1				1
Bacterial	Medical	5	1	1	3			
	PK	1	1					
Fungal	Medical	2				2		
	PK	1			1			
HSV	Tissue adhesive	2			2			
	PK	2	1	1				
HZV	LK	1			1			
Rosacea	Medical	1		1				
	Tissue adhesive	1	1					
Entropion	PK	1				1		
Exposure	Tissue adhesive	1						1
	PK	2			1	1		
	Evisceration[a]	2						2
Staph. hypersen.	Tissue adhesive	1					1	
Corneal ulcer (unknown cause)	Medical[b]	1						
	PK	1	1					
	Enucleation[a]	1						1

[a] Blind painful eye.
[b] Down syndrome.
KCS, keratoconjunctivitis sicca; HSV, herpes simplex virus; OCP, ocular cicatricial pemphigoid; HZV, herpes zoster virus; PK, penetrating keratoplasty; LK, lamellar keratoplasty.

TABLE 6. *Treatment and final best corrected visual outcome*

Treatment	Number	Gain ≥2	Gain 1	0	Loss 1	Loss ≥2	NLP
Medical	12	1	4	4	2	0	1
Tissue adhesive	14	5	1	4	1	2	1
Tissue adhesive → PK	1	0	0	1	0	0	0
PK/LK	(8/1)	3	1	2/1	2	0	0

PK, penetrating keratoplasty; LK, lamellar keratoplasty; NLP, no light perception.

from 2 to 30 days, with a mean of 8.8 days. Nine eyes developed repeated perforations. These subsequent perforations were excluded from further evaluation. PK was used when the perforation could not be glued and the visual potential was good. PK was performed in eight eyes. Of these eight, four eyes (50%) improved in BCVA and four eyes achieved a clear graft. Lamellar keratoplasty was used in one eye. In cases of RA, medical management included systemic immunosuppression in some patients. Two

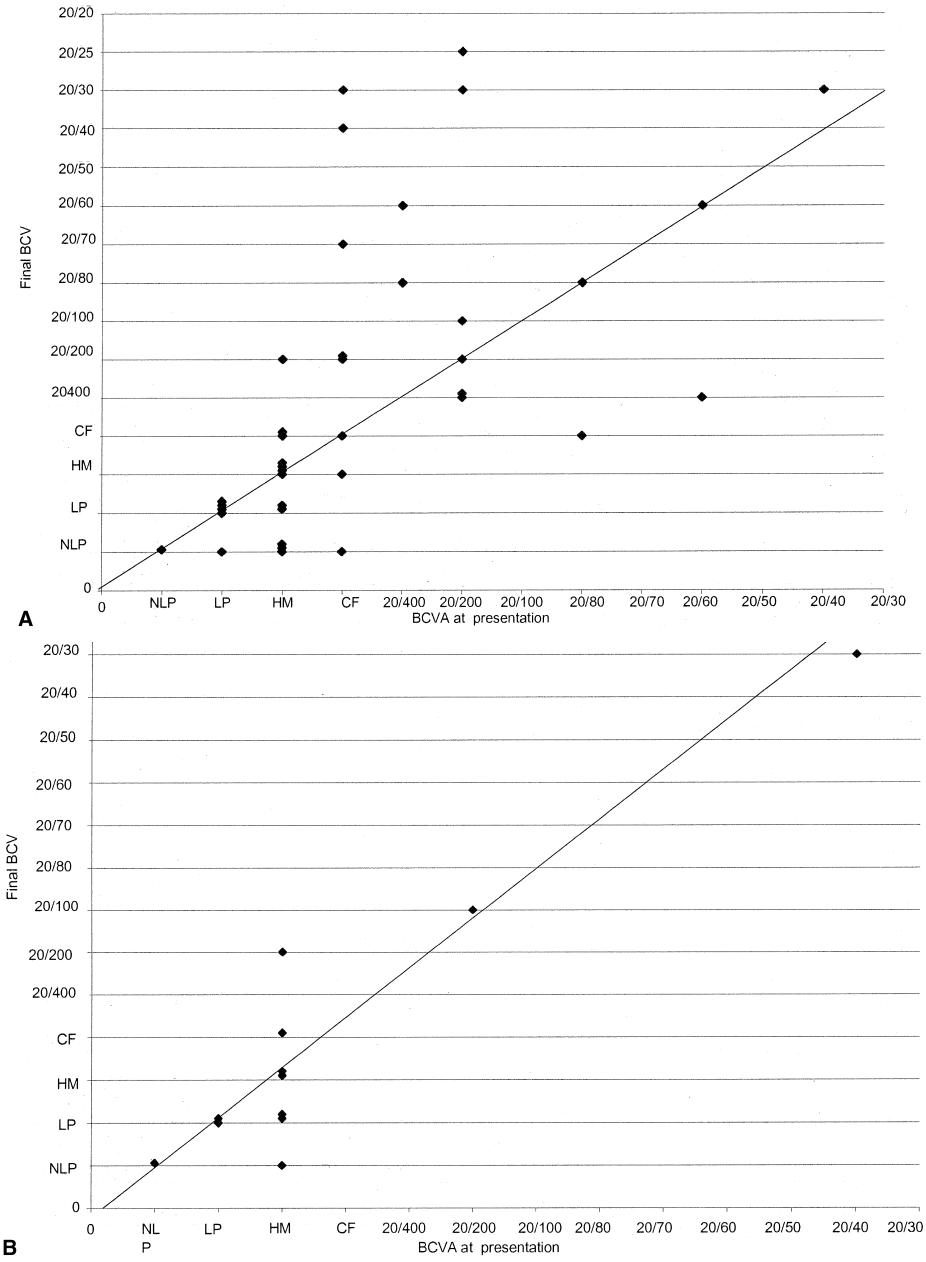

FIG. 2. BCVA at presentation vs. final BCVA. **(A)** Combined graph. **(B)** Medical treatment.

blind painful eyes were eviscerated, and one blind painful eye was enucleated after successful treatment of the perforations (Table 5). The initial and final BCVA demonstrated a statistically significant direct relationship for all therapies combined.

Visual acuity improved ≥2 Snellen lines in 3 of 8 eyes (37.5%) treated with PK, in 5 of 14 eyes (35.7%) of those treated with tissue adhesive, and in 1 of 12 eyes (8.3%) of those treated medically (Table 6). The final BCVA after the treatment of 15 (37.5%) of nontraumatic corneal perforations was improved (Fig. 2).

DISCUSSION

In this study, the etiologies of nontraumatic corneal perforations included sterile corneal ulcers (23 patients, 57.5%) that are most commonly associated with a) KCS and RA, b) exposure keratopathy, c) neurotrophic keratopathy (HSV in 4 patients and herpes zoster virus in 1 patient), as well as bacterial and fungal corneal ulcers (9 patients, 22.5%). KCS is the most common cause of nontraumatic corneal perforation in this study (12 of 40 eyes,

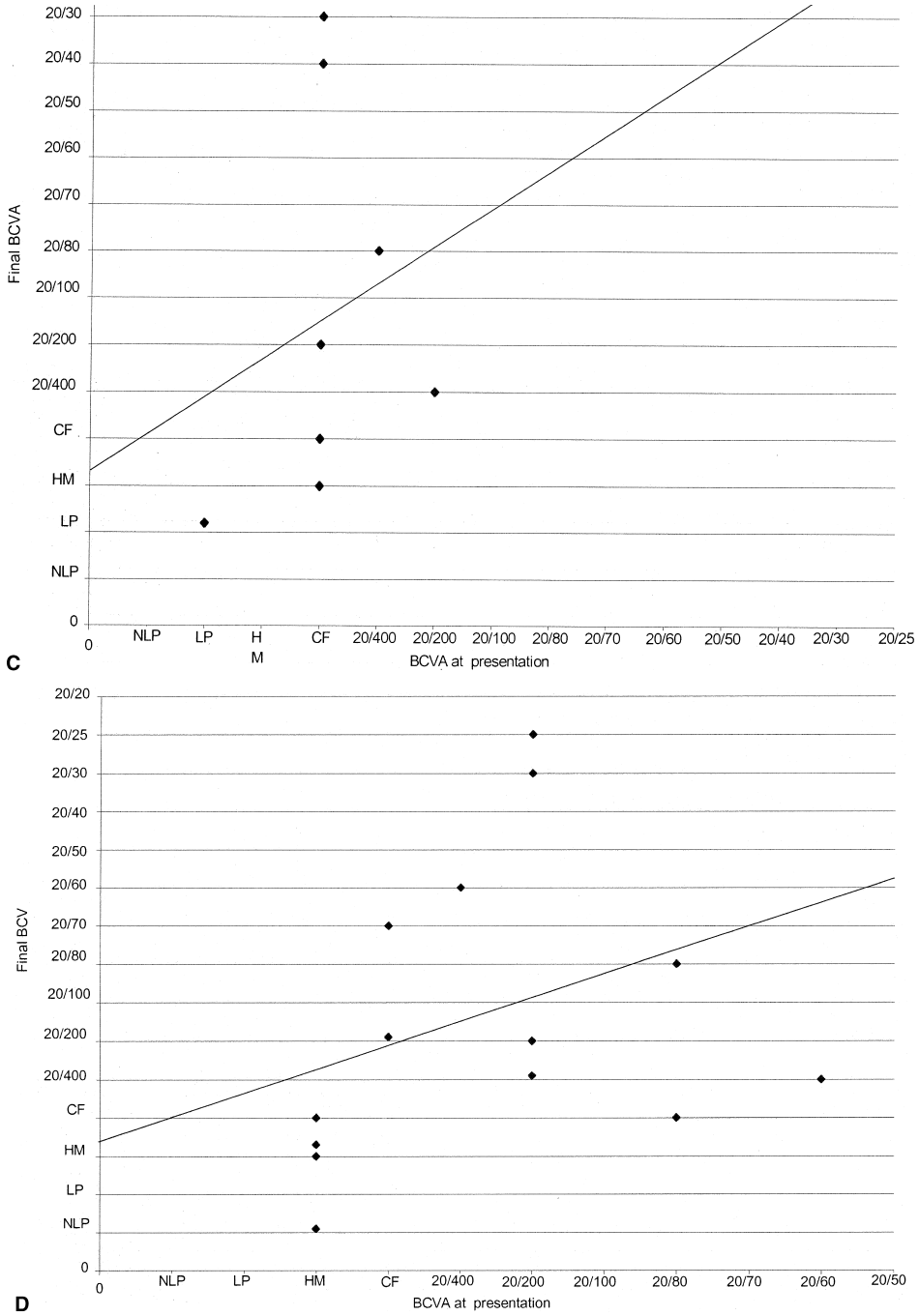

FIG. 2. BCVA at presentation vs. final BCVA. **(C)** PK. **(D)** Tissue adhesive.

30%). Women were more frequently affected by this problem than men (seven of nine patients, 77.8%). We found RA to be the most common underlying condition associated with KCS-related corneal perforation (five of nine patients [55.6%], four women and one man). The ages ranged from 49 to 73 years, with a mean of 65.4 years. RA is the most common collagen vascular disorder that involves the ocular surface.[7] Women are primarily affected. Of RA patients, 24–31% have Sjögren's syndrome.[8]

When a patient presents to an ophthalmologist with a corneal perforation associated with KCS, advanced RA is usually evident. Keratolysis is the mechanism of corneal perforation in these patients.[9] In most cases, severe aqueous tear deficiency is found. The superficial layers of the cornea begin to ulcerate and a descemetocele may develop and be followed by perforation.[10] Dry eyes should be treated aggressively in RA patients. Frequent lubrication, punctal occlusion, and tarsorrhaphy may be useful in promoting reepithelialization. Immunosuppressive agents may be useful in alleviating the immunologic process responsible for the corneal melting.[11]

This study demonstrated a statistically significant direct correlation between presenting and final BCVA for the aggregate of all treatment types ($R^2 = 0.38$, $p = 0.0001$, Fig. 2). That is, the better the presenting vision, the better the final vision after therapy. We found no statistically significant correlation between treatment modality and final visual acuity after adjusting for varying presenting visual acuity (Figs. 2A–C). However, biases existed in this study. The underlying disease and visual potential did influence the treatment modality. Consequently, the varying presenting visual acuity, associated with different diagnoses, confounded the outcome of therapy.

The objective in treating a patient with a corneal perforation is to restore the integrity of the globe and useful vision. This goal may require a sequence of procedures. The goals of initial intervention are to close the perforation and restore the integrity of the globe. This should be done as rapidly as possible to minimize peripheral anterior synechiae and risk of cataract formation and intraocular infection.

Tissue adhesive works well when the corneal perforation is ≤1.0 mm in diameter at the level of Descemet's membrane, away from limbus, and is concave in shape with a crater for the tissue adhesive. In many cases, adhesive is sufficient treatment that promotes healing and scarring while obviating the need for further surgery. Tissue adhesive is left in place for several months until it dislodges spontaneously. Adhesive has been shown to be bacteriostatic to gram-positive (but not to gram-negative) organisms, especially during polymerization.[12] Tissue adhesive has also been shown to slow stromal-melting,[13] possibly by preventing invasion by tear-borne inflammatory cells. Adhesive supports the stroma tectonically through vascularization and fibroplasia.[14] Tissue adhesive is not an option for large corneal perforations (>2 mm in diameter) or in anterior bulging corneal perforations.

In our experience, the application of tissue adhesive was often sufficient to promote adequate healing without surgery. Many surgeons recommend keratoplasty following tissue adhesive applications.[15] In this study, tissue adhesive was applied in 15 eyes; 14 eyes (93.3%) achieved tectonic stability and 6 (42.8%) improved in final BCVA. Only 1 of 15 eyes required a PK because the perforation was not sealed by tissue adhesive.

Medical treatments can be effective in the management of small perforations (≤1 mm in diameter) without iris prolapse. However, in these cases, the time to resolution of the leak may be prolonged. Medical therapy was used when application of tissue adhesive was not feasible because of an ectatic perforation and/or active infection. In pinpoint or small perforations, patching may be effective if stromal swelling seals the perforation and there is no infection. We used topical or systemic hypotensive agents to diminish the flow of aqueous humor and to promote closure of the tissue defect.[16]

Using medical treatment, we were able to achieve tectonic stability in 13 eyes (32.5%). Final BCVA was improved in 5 of 12 eyes (41.6%). Visual acuity was not measured in one case because the patient had Down's syndrome. If there was no contraindication to medical treatment, we used this treatment for infectious corneal perforation first because the outcome of surgical treatment is suboptimal when the infection is uncontrolled. Perforations are also frequently ectatic in this setting.

Larger central perforations (>1 mm in diameter) should be treated with PK as initial therapy if the visual potential is good. We believe that patients with microbial keratitis should be treated aggressively with topical fortified antibiotics for a period of 24–48 hours before PK. Corneal transplantation in a perforated cornea is technically difficult, and the possibility of injuring other anterior segment structures is always present. Although the anatomic success in our keratoplasty series was high, only four of eight (50%) achieved a clear graft. The success of PK in the treatment of corneal perforation depends on the timing of surgery and the cause of the perforation. Ideally, PK is deferred until the eye is quiet. However, this is frequently not possible when the perforation cannot be glued or does not respond to medical therapy. If the visual acuity after tissue adhesive was poor because of scarring, a PK could be performed at a later date when the inflammation had subsided. However, in our experience, this was usually not necessary. Corneal transplantation was not recommended in patients with perforations successfully managed medically or with tissue adhesive because of the poor prognosis associated with severe ocular surface disease and, in some cases, preexisting posterior segment pathology.

Finally, we can decrease the incidence of nontraumatic corneal perforation by early detection and aggressive treatment of ocular surface conditions including KCS, HSV, and herpes zoster virus neurotrophic keratopathy, exposure keratopathy, and rosacea. In addition, these underlying diseases must be treated after perforation to decrease the likelihood of recurrent problems and to improve the outcome of PK.

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