

# The Efficacy of Fibrin Glue in Corneal Perforations

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## Abstract

**Purpose:** To determine the efficacy of fibrin glue in corneal perforations up to 3 mm in diameter

**Methods:** A case series study was performed on corneal perforations up to 3 mm who were admitted at Farabi Hospital- Tehran. Age, visual acuity, presence and size of corneal thinning, corneal epithelial defect, size and depth of corneal infiltration, site and size of corneal perforation, corneal vascularization, anterior chamber depth and reaction and the etiology of corneal perforation were recorded. Then corneal perforation was sealed by using of fibrin glue and soft contact lens and the patients were followed for at least 3 months.

**Results:** Of 18 patients, 8 patients were female and 10 patients were male. Mean age was 52±25.7 years. Size of corneal perforations were 0.6 to 3 mm (mean=1.88 mm). The etiologies of corneal perforation were postinfectious in 11 and noninfectious in 7 cases. Fifteen eyes (83.3%) had successful healing of corneal perforation after 3 months. All the cases who failed had corneal perforation greater than 2 mm in diameter. Success rate was significantly lower in corneal perforation > 2 mm in diameter. No case developed giant papillary conjunctivitis or secondary glaucoma. Only one (5.6%) eye showed a significant increase in deep corneal vascularization.

**Conclusion:** Fibrin glue is effective in the closure of corneal perforations up to 2 mm in diameter. Corneal perforation > 2 mm in diameter may not respond well. It provides fast healing with low rate of corneal vascularization.

**Keywords:** corneal perforation, fibrin glue, keratitis, vascularization

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## Introduction

Corneal perforations require urgent management to reduce subsequent ocular morbidity. Simple patching<sup>1</sup> and soft contact lenses<sup>2</sup> promote healing of self-sealed perforations. Conjunctival flaps<sup>3</sup> are rarely helpful in the healing of corneal perforations. Penetrating keratoplasty (PK) for corneal perforations has technical difficulties in the presence of inflammation.<sup>3-5</sup> Adhesives has been used for sealing of corneal perforations and seems to be efficient.<sup>3</sup>

The various types of tissue adhesives can be subdivided into synthetic adhesives (eg, cyanoacrylate derivatives) and biologic adhesives (eg, fibrin-based adhesives).<sup>6,7</sup> Some studies by Hirst et al,<sup>8</sup> Kenyon,<sup>9</sup> and Weiss et al<sup>10</sup> have revealed the benefits of cyanoacrylate tissue adhesives (CTAs), a nonbiodegradable tissue adhesive, in the setting of corneal perforation or progressive thinning, with lower rates of PK, conjunctival flap surgery, and enucleation. But it may induce an inflammatory foreign body reaction, including neovascularization and tissue necrosis.<sup>3,11</sup>

Fibrin glue (FG), being biologic in nature, is biocompatible and completely biodegradable. It induces minimal stromal inflammation and foreign body reaction, neovascularization and no tissue necrosis, but has lower strength.<sup>12,13</sup> Lagoutte et al<sup>12</sup> and Sharma et al<sup>3</sup> have used fibrin glue to seal perforated corneal ulcers with favorable results.

In the 1990s, fibrin was combined with aprotinin to retard the dissolution of the fibrin adhesion. Now, Tisseel VH Fibrin Sealant (Baxter Healthcare Corporation, Glendale, CA) is a commercially available fibrin adhesive approved by the U.S. Food and Drug Administration as an adjunct to hemostasis in cardiopulmonary surgery bypass and in treatment of splenic injuries, but not for ocular surgery.<sup>14</sup>

A few studies in which this adhesive was used for sealing corneal perforations indicated that it was efficient, well tolerated, and did not cause inflammation,<sup>6</sup> But most of them were case reports. We conducted an interventional study to evaluate the efficacy of Tisseel VH Fibrin Sealant in corneal perforation.

## Methods

18 patients (18 eyes) treated for corneal perforation between May 2005 and December 2005 at the Farabi Eye Hospital, Tehran, Iran were included in this study. The study was reviewed and approved by the ethics committee of the Medical Faculty of Tehran University of medical sciences, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written consent was obtained from all patients.

The clinical diagnosis of corneal perforation was based on the presence of visible corneal perforation, a shallow anterior chamber and confirmed with a positive Seidel's test. Inclusion criteria were corneal perforations up to 3 mm in diameter with either no infiltrate or resolving infiltrates. Exclusion criteria were anterior staphyloma, and progressive corneal infiltrates, and stromal melting because of underlying collagen vascular disorders.

All patients underwent complete ocular examination. Slit-lamp biomicroscopy was performed and the presence and size of the epithelial defect (if any); size and depth of infiltrates; corneal thinning; site, size, and location of corneal perforation; and superficial or deep corneal neovascularization were recorded.

Corneal scrapings were obtained from the margin of the infiltrate in cases with active keratitis, and direct microscopy and cultures were performed. On the basis of clinical examination and microbiologic tests, intensive antimicrobial therapy was prescribed in each case. In patients with active keratitis who developed perforation, tissue adhesive was applied only when they either showed clinical response to antimicrobial therapy or microbiologic tests did not reveal any microorganisms. Patients showing progression in infective keratitis despite of treatment were considered for therapeutic penetrating graft.

## Surgery

Only one surgeon performed all the procedures. The tissue adhesive was reconstituted according to the manufacturer's instructions. Topical anesthesia was used in all patients. Speculum was inserted to obtain adequate exposure of the ocular surface. Under the operating microscope, necrotic

tissue was removed from the site of perforation. The area surrounding the corneal perforation was de-epithelialized and kept dry with a cellulose sponge. Intracameral injection of methyl cellulose was performed and the reconstituted adhesive was applied at the site of perforation. The glue was then left undisturbed for about 30 seconds, during which time it was transformed into a translucent whitish plug. At the end, a Seidel's test was performed to check for any leakage and bandage contact lens was applied.

Patients were followed at 1 day, 2 days, 3 days, 1 week, 6 weeks, 3 months, and then every 3 months. At each follow-up, anterior chamber depth, inflammatory reaction, and glue adherence were recorded. Seidel's test was performed to discover leakage. Repeated tissue adhesive application was performed if Seidel's test was positive. If the patients required more than 2 applications, or showed an increase in the size of perforation beyond 3 mm in diameter, or an increase in the size of the infiltrate, therapeutic penetrating keratoplasty was considered. Healing of the corneal perforation was considered the primary outcome measure and reported.

Data were analyzed by SPSS 10.0.1 (SPSS Inc, Chicago, Illinois, USA). Success rates in different groups were compared using Chi-square and Fisher's exact test.

## Results

Eighteen eyes of 18 patients were included in the study. The mean age of the patients was 52 years (range, 1–85 years). The study included 10 (56.6%) men and 8 (44.4%) women. Corneal perforation was in right eye in 8 (44.4%) patients and in left eye in 10 (56.6%).

The most common etiology of corneal perforation was postinfective in 11 (61.1%) eyes, of which 7 (38.9%) developed corneal perforations after bacterial keratitis, and 4 (32.2%) after herpes simplex keratitis. There was no case of corneal perforations after fungal keratitis. Noninfective corneal perforations were observed in 7 (38.9%) eyes, including chemical burn (n=3, 16.7%), neurotrophic perforations (n=1; 5.6%), posttraumatic perforations (n=1; 5.6%), Mooren's ulcer (n=1; 5.6%), and Graft Versus Host Disease (GVHD) (n=1; 5.6%) (Table 1).

**Table 1:** Etiology and Size of Corneal Perforations

	No (%)
<b>Etiology</b>	
<b>Post infectiuous</b>	11 (61.1%)
bacterial	7 (38.9%)
Hepes simplex	4 (32.2%)
<b>Non infectiuos</b>	7 (38.9%)
Chemical burn	3 (16.7%)
GVHD	1 (5.6%)
Neurotrophic	1 (5.6%)
Mooren's ulcer	1 (5.6%)
posttraumatic	1 (5.6%)
<b>Size (mm)</b>	
≤ 0.5	0
0.6-1	5 (27.8%)
1.1-2	8 (44.4%)
2.1-3	5 (27.8%)

The corneal perforations ranged from 0.6 to 3 mm in diameter. Most of the corneal perforations in our study (44.4%) were 1.1 to 2 mm in diameter (Table 1). All of our cases were acute (the duration of corneal perforations were less than two weeks). Mean duration of perforation was 3.8 days. Additional procedures during the application of tissue adhesive were required in 4 (22.2%) eyes. Hyaluronate was used in these eyes with iris presenting at large perforation site.

At the first follow-up at 24 hours, the anterior chamber was formed, and Seidel's test was negative in all cases. FG was present in anterior chamber in 2 patients that was resolved after 2 to 3 days without any complication like inflammation or glaucoma. At 3 days of follow-up, Seidel's test was positive in 1 eye with herpetic keratitis. PK was performed for this case.

At 6 weeks, Seidel's test was positive in 3 other eyes (one with herpetic keratitis after discontinuing of systemic acyclovir and recurrence of herpetic keratitis, one with GVHD, and one with chemical burn). Positive Seidel's test was managed by reapplication of the FG in GVHD. Scleral patch graft was

performed in the other 2 cases because of large corneal perforations.

None of the eyes had a positive Seidel's test at 3 months' follow-up, but a one year old boy who was operated because of corneal perforation due to bacterial keratitis developed corneal scar that needed PK. Successful healing of corneal perforation was observed in 15 (83.3%) of 18 at 3 months' follow-up. All the cases who failed had corneal perforation >2 mm. Success rate was significantly lower in corneal perforation  $\leq$  2 mm. ( $P=0.009$ , Table 2) There was no significant difference in success rate between postinfectious and noninfectious groups (81.8% vs. 85.7% respectively,  $P=0.67$ ).

**Table 2:** Success rate in different size of perforation

Size (mm)	No (%)
0.6-1	5.5 (100%)
1.1-2	8.8 (100%)
2.1-3	2.5 (40%)*

\* Chi square test:  $P=0.009$

The mean duration of fibrin glue adherence in group 1 was 11 days (range, 8–14 days). None of the eyes had residual glue at the end of 3 months. All the patients had visual acuity of less than  $20/200$  at presentation. Seven eyes (38.9%) had visual acuity improvement after 3 months but none of them reached visual acuity of more than  $20/200$ .

Only one eye (5.6%), with herpetic keratitis had an increase in the size of infiltrate, necessitating a therapeutic penetrating graft. No case developed giant papillary conjunctivitis or secondary glaucoma. Only one (5.6%) eye showed a significant increase in deep corneal vascularization.

## Discussion

Our study showed that fibrin glue was effective and safe in the healing of corneal perforations. Fibrin glue was effective in 83.3% of the corneal perforations in our study. Lagoutte et al<sup>12</sup> reported a 93% success rate for closure of corneal perforations up to 2 mm after application of fibrin glue. In our study 27.8% of patients had corneal perforation greater than

2 mm, but the success rate was comparable. Moreover, Sharma et al<sup>3</sup> showed that fibrin glue was effective (success rate: 78.9%) in the closure of corneal perforations up to 3 mm in diameter, but most of the perforations in his study (68.3%) were <1 mm in diameter. He compared the efficacy of fibrin glue and CTA in corneal perforations and concluded that fibrin glue and CTA were both effective in the closure of corneal perforations.

In our study, 11 (61.1%) cases of corneal perforations occurred after infective keratitis. The higher incidence of corneal perforations due to an infective etiology can be directly correlated with the higher incidence of infective keratitis in the most countries.<sup>3,15,16</sup>

In our patients, both postinfective and noninfective corneal perforations responded well to fibrin glue. There was no significant difference in success rate between postinfective and noninfective groups. It was successful in all cases with bacterial keratitis but only 50% of cases with herpetic keratitis responded well. In Sharma et al study<sup>3</sup> only 5.0% of cases had herpetic keratitis.

Several factors, including size, chronicity, and presence of infiltrate, have been reported to affect the outcome of tissue adhesive application in corneal perforations. In various studies, tissue adhesives have been applied for corneal perforations varying from 0.5 to 3 mm in diameter.<sup>1,4,5,16-18</sup> In this study, we included patients with corneal perforations up to 3 mm in size. Fibrin glue was effective for corneal perforations 0.6 to 1 mm, and 1 to 2 mm. Corneal perforations with the size of 2 to 3 mm were relatively more difficult to manage. We demonstrated a significantly higher success rate in corneal perforation  $\leq$  2 mm than greater than 2 mm. Like Sharma's study<sup>3</sup> all the cases who failed had perforation > 2 mm diameter.

It has been reported that chronic perforations may be resistant to treatment with tissue adhesive application because of incomplete removal of the epithelialized tract.<sup>3</sup> All of our cases were acute; this might be a reason for our good results. It seems that early diagnosis and emergent management will improve the success rate.

In our study duration of FG adherence and the time of epithelialization were less than what was reported for CTA in previous studies.<sup>3,18</sup> Moreover, FG seems to be safe

and biocompatible; because in two eyes we observed FG in anterior chamber postoperatively that resolved without any complication such as glaucoma, corneal edema or inflammation. We had no cases of giant papillary conjunctivitis, despite what was reported for CTA<sup>3</sup> (36.4%). This can be related to the more regular surface subsequent to FG application. Only one of our patients developed corneal vascularization. This is one of advantages of FG especially

when it is used as a temporary measure, before PK.

### Conclusion

In summery, although we report our experience with only a small number of patients and limited follow-up time, using FG for corneal perforation < 2 mm in diameter seems to be satisfactory with no major complications and low rate of corneal vascularization.

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