Evaluation of Cyanoacrylate Tissue Adhesive Glue Application Outcomes in Corneal Thinning and Perforation

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Objectives: Corneal thinning and perforation are ocular emergencies necessitating urgent intervention to prevent visual impairment or enucleation. Cyanoacrylate tissue adhesive is frequently used to maintain globe integrity in these cases. However, gaps remain in understanding the outcomes of corneal gluing and the factors influencing its efficacy. This case series evaluates the clinical characteristics and outcomes of glue application in corneal thinning and perforation.

Methods: A retrospective chart review was conducted on patients treated for corneal thinning and perforation at the University of Florida between January 2012 and May 2023. Demographic data, clinical history, glue application details, and posttreatment outcomes were collected and analyzed.

Results: The study included 128 eyes from 125 subjects. Corneal perforation was found in 71 eyes (55.5%), mostly centrally (49.2%). The leading cause of perforation/thinning was microbial infection (45.3%). The average number of glue applications per eye was 1.66. Within 1 month, 23 patients (18.0%) required only glue reapplication, 37 (28.9%) required surgical intervention (regardless of glue reapplication), and 68 (53.1%) required no further treatment. Factors significantly linked to gluing failure (requiring surgery within 1 month) in univariate analysis included large perforation size, microbial infection, ocular surface disorder, single glue application, and indirect application via sterile drape. Multivariate analysis showed that only large perforation size was significantly associated with gluing failure.

Conclusion: Corneal glue application is an effective temporizing measure for corneal thinning and perforation, with multiple applications potentially providing added stability to the globe. However, the need for surgical intervention is high.

Key Words: Corneal glue—Corneal perforation—Corneal thinning.

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Corneal thinning and perforation are a significant cause of ocular morbidity that requires immediate intervention. Etiologies are diverse and can arise from infectious, traumatic, immune, and neurotropic causes, among others. Without appropriate assessment and intervention, these can result in loss of vision, endophthalmitis, and even enucleation.[1] Management strategies depend on the etiology, location, and size and include treatment of the cause and reconstitution of corneal structural integrity, such as placement of a bandage contact lens, application of tissue adhesives, and surgical interventions ranging from corneal patch graft to penetrating keratoplasty.[1,2]

Cyanoacrylate tissue adhesive (CTA) is commonly used, although off-label, as first-line therapy for the acute management of corneal thinning and perforation, especially in cases where surgery is not immediately needed or available. Cyanoacrylate tissue adhesive is a combination of cyanoacetate and formaldehyde, which increases in tectonic strength on contact with fluid via polymerization.[3] Corneal glue can be applied via two main methods: direct and indirect via a trephined drape.[4] Direct application involves drying the wound, aspirating CTA into a dropperette or syringe, and painting the lesion with the glue so that the defect is filled on expansion. In indirect application, the wound is dried and glue is placed on a piece of surgical drape cut to fit the lesion, and the drape is subsequently placed over the defect so that the edges adhere.[4]

Cyanoacrylate tissue adhesive application has been shown to be an effective treatment option for improving the visual outcomes of patients with corneal pathologies, preventing the need for further surgery, facilitating significant corneal healing, and even decreasing enucleation rates from 19% to 6%.[5,6] In addition, research has demonstrated that early use of CTA has antikeratolytic and bacteriostatic properties, further aiding in the treatment of corneal perforations.[7–9] Corneal glue application does not address underlying pathology, and thus additional interventions are often needed.

Although the use of corneal glue has been demonstrated to effectively aid in the treatment of corneal pathologies, the literature describing corneal gluing outcomes is poor and outdated. For example, studies have reported particularly varied rates of "success" with gluing, ranging from 28% to 91%.[10–12] In addition, there is a paucity of data on the clinical factors associated with corneal gluing effectiveness and failure. In this case series, we evaluate the clinical characteristics and outcomes of corneal gluing use in corneal thinning and perforation at the University of Florida from 2012 to 2023.

METHODS

This protocol (IRB202300796) was approved by the Institutional Review Board of the University of Florida and adhered to the Declaration of Helsinki.

A retrospective review of the electronic medical record was performed on all patients treated for corneal thinning and perforation with corneal glue application between January 2012

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and May 2023. Patients were identified using current procedural terminology codes through the University of Florida's integrated data repository research services. Charts with incomplete data or no follow-up after initial presentation for corneal gluing were excluded.

The following data were captured: demographic information (gender, age), systemic conditions, detailed ophthalmic history, systemic and ophthalmic medications, ophthalmic comorbidities, best-corrected distance visual acuity at presentation (measured in logMAR), intraocular pressure (intraocular pressure; measured in mm Hg), ocular examination including anterior chamber (AC) depth (with typical AC depth at ~3.0 mm, deep AC is defined as ≥2.0 mm depth, flat AC is defined as lens and/or iris corneal touch with complete lack of AC depth, and shallow AC falling in between deep and flat), etiology, location of perforation/thinning, size of the perforation/thinning, glue application method, total number of glue applications, bandage contact lens use after gluing, the need for medical and surgical treatments after gluing, and the final outcome (complications, best-corrected visual acuity [BCVA]) at 1 and 3 months, and IOP at 1 and 3 months). Thinning/perforations greater than 6 mm^2 were qualified as large. Each eye was considered as one record. All data analyses were conducted in JASP version 08.18.3, and two-sided *P* values of less than 0.05 were considered statistically significant.

To examine the success of single versus multiple applications of corneal adhesives, Kaplan–Meir survival analysis was conducted. For eyes that underwent only one glue application, the gluing was considered successful when the globe remained intact without the need for additional gluing or surgical intervention. For eyes that underwent multiple glue applications, subsequent applications of glue after initial gluing were recorded as a single event, regardless of how many additional instances in which glue was applied. If subsequent surgical intervention was necessary, each surgery was considered an additional event.

To assess factors associated with gluing failure, logistic regression models were used. Glue failure was defined as an open globe in need of surgical intervention within 1 month of the initial gluing, regardless of the total number of corneal glue applications. One month was used as an arbitrary time point because glue application is often used as a temporary measure to secure the globe for future surgical intervention. Univariable analyses were performed using the following variables: age, sex, systemic conditions, systemic autoimmune conditions, use of systemic immunosuppression, significant ocular surface diseases, use of ophthalmic steroids, location, size, and etiologies of perforation/thinning, bandage contact lens type used, and total number of times glue was applied.

In the multivariable regression model, metrics including large perforation/thinning size (as opposed to small), perforation (as opposed to thinning), peripheral location (as opposed to central), microbial cause (as opposed to other causes), and single glue application (as opposed to multiple) were incorporated because of their clinical significance and to avoid model overfitting.

RESULTS

Chart review identified 125 subjects and 128 eyes that met the inclusion criteria. The baseline demographic and clinical characteristics of included subjects are shown in Table 1, with a median age of 64 years old and 58 females (45.3%). A total of 86 (67.2%) patients had a systemic condition, with hypertension, diabetes, and cancer being the most common. Autoimmune disease was present in 14 patients (10.9%), with Sjogren syndrome as the most common. Thirty-four patients (26.6%) were on systemic immunosuppression, with the majority on oral corticosteroids. Ocular surface disorder was present in 51 patients (39.8%), with neurotrophic keratopathy and dry eye disease as the two most common. Fifty-two patients (40.6%) were taking an ocular corticosteroid. In addition, most patients were taking an antimicrobial (96 patients, 75%), with antibacterial as the most common type (92; 71.9%), and 35 patients (27.3%) were on glaucoma medications.

TABLE 1. *Demographic and Clinical Features of 125 Subjects and 128 Eyes at Initial Presentation*

Age, Median (Range)	64.03 (7.56–97.59)
Sex (%)	
Female	58 (45.3)
Male	70 (54.7)
Laterality (%)	
Right eye number	63 (49.2)
Left eye number	65 (50.8)
Presence of systemic condition, number (%)	
Hypertension	68 (53.1)
Autoimmune disease	14 (10.9)
Non-Sjogren	5 (3.9)
Sjogren	11 (8.6)
Cancer	23 (18.0)
Diabetes	24 (18.8)
Thyroid disease	10 (7.8)
Alcohol abuse	12 (9.4)
Cocaine abuse	1 (0.8)
Presence of ocular surface disease, number (%)	
Eye lid disorder	8 (6.25)
Neurotrophic keratopathy	17 (13.3)
Dry eye disease	15 (11.8)
Stevens–Johnson syndrome/toxic epidermal necrolysis/mucous membrane pemphigoid	6 (4.7)
Others	16 (12.5)
Use of systemic immunosuppression, number (%)	
Oral corticosteroid	30 (23.4)
Nonsteroidal immunosuppressive	10 (7.8)
Use of ophthalmic medication, number (%)	
Corticosteroid	52 (40.6)
Topical	51 (39.8)
Subconjunctival	1 (0.8)
Antimicrobial	96 (75)
Antibiotic	92 (71.9)
Antiviral	17 (13.3)
Antifungal	16 (1.25)
Antiglaucoma	35 (27.3)
Cycloplegic	26 (20.3)
Oral doxycycline	23 (18.0)
Nonsteroidal anti-inflammatory drugs (topical)	2 (1.6)
Cyclosporine 0.9%	10 (7.8)
Nonsteroidal anti-inflammatory drugs (systemic)	15 (11.8)
Preservative-free artificial tears	23 (18.0)

AC, Anterior chamber; BCVA, best-corrected visual acuity; CTA, cyanoacrylate tissue adhesive; IOP, intraocular pressure.

Table 2 shows the clinical characteristics of corneal perforation/thinning and corneal glue application. Corneal perforation was present in 71 eyes, with 29 cases Seidel negative because of iris plugging. Most eyes had central (63) or paracentral (37) lesions, with a median area of perforation/thinning of 9.75 mm^2. The AC was deep in 47 eyes before gluing. Etiology of corneal thinning and perforation was microbial in 58 eyes, with bacterial (47) and fungal (13) as leading microbial causes. Other leading causes were sterile melt (21), laceration or mechanical trauma (18), and

TABLE 2. *Clinical Features of Corneal Perforation/Thinning and Corneal Glue Application*

Initial presentation (%)	
Descemetocele	49 (38.3)
Perforation (Seidel positive)	42 (32.8)
Perforation (Seidel negative, plugged with iris)	29 (22.7)
Thinning	32 (25)
Causes of perforation or thinning, number (%)	
Microbial	58 (45.3)
Bacterial	47 (36.7)
Fungal	13 (10.2)
Viral	7 (5.5)
Rheumatoid associated	2 (1.6)
Neurotrophic keratitis	19 (14.9)
Laceration	18 (14.1)
Surgical wound	7 (5.5)
Peripheral ulcerative keratitis	7 (5.5)
Exposure keratopathy	5 (3.9)
Keratoprosthesis melt and extrusion	3 (2.3)
Burn (alkali, acid and electrical)	1 (0.8)
Suture leak	1 (0.8)
Vitamin a deficiency	1 (0.8)
Other sterile melts	19 (14.8)
Location of perforation/thinning	
Central	63 (49.2)
Paracentral	37 (28.9)
Peripheral	28 (21.9)
Anterior chamber (AC) before gluing	
Deep	47 (36.7)
Flat	28 (21.9)
Shallow	26 (20.3)
Median size of perforation/thinning in mm^2 (interquartile range)	9.75 (2.13–19.56)
Total number of CTA application per eye	
Mean (SD)	1.66 (1.06)
Median (range)	1 (1–9)
Median BCVA at time of CTA application in logMAR (range)	2.3 (0–3)
Median IOP at time of CTA application in mm Hg (range)	7 (1–45)
Median BCVA 1 mo after CTA application in logMAR (range)	2 (0–3)
Median IOP 1 mo after CTA application in logMAR (range)	10 (3–33)
Median BCVA 3 mo after CTA application in logMAR (range)	2 (0–3)
Median IOP 3 mo after CTA application in logMAR (range)	12 (2–40)

neurotrophic keratitis (19). Multifactorial etiology was present in 19 eyes. Within 1 month of corneal gluing, 23 patients required only glue reapplication, 37 patients required surgical intervention (regardless of glue reapplication), and 68 patients required no further treatment. The average number of glue applications per eye in the study was 1.66. Mean BCVA before and after glue application were 2.3 and 2.3 (Wilcox paired sample *t* test, $P=0.235$). The median days of glue retention in this study was 50.5 days, with a maximum glue retention of 1,493 days. One eye in our series, with significant ectatic corneal disease and malignant glaucoma with a surgical history of many trabeculotomy and tube shunt procedures, underwent a total of nine corneal glue applications.

Figure 1 shows Kaplan–Meier survival curve for single versus multiple glue applications, with success defined as an intact globe not requiring surgical intervention. Survival was longer for the multiple glue application cohort, although this difference was nonsignificant (Log-rank Mantel–Haenszel, $P=0.056$). Survival percentages for single application and multiple glue application at 10 days, 30 days, and 90 days were 73.3%, 62.7%, and 50.7% and 92.4%, 83%, and 71.7%, respectively. Odds ratio (OR) of failure (globe requiring surgery) for single versus multiple application at 10, 30, and 90 days were 3.53, 2.20, and 1.74, respectively. The OR for failure for single versus multiple corneal glue applications diminishes considerably but from 10 days (OR=3.52) to 3 months (OR=1.74).

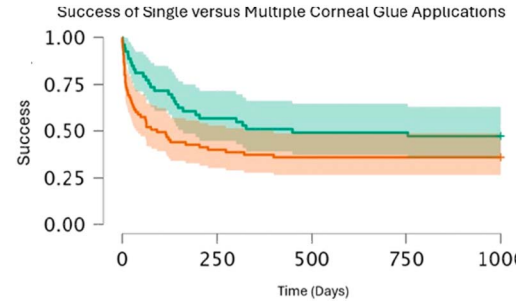

FIG. 1. Kaplan–Meir analysis showing survival (measured as success, which is an intact globe not requiring surgical intervention) for single (orange line) and multiple (green line) corneal glue application. Log-rank Mantel–Haenszel, $P=0.056$.

Univariate analysis of factors associated with gluing application failure (Table 3) was conducted. A larger size of perforation, microbial etiology, presence of ocular surface disorder, single glue application, and indirect application via trephined sterile drape were significantly associated with glue application failure. Monomicrobial versus polymicrobial cause did not significantly affect gluing success at 1 month.

In the multivariate logistical regression model (Table 4), only large perforation size (OR=10.296; CI=2.11–49.781; $P=0.004$) and single glue application (OR=5.261; CI=1.109–24.949; $P=0.037$) were significantly associated with glue failure. No significant association was seen with the following variables: perforation (versus thinning), peripheral location (versus central), and microbial etiology (versus all others).

Complications within 1 month (Table 5) were recorded in 48 eyes, with neovascularization as the most common complication (28). Surgical interventions were performed in 37 eyes, with penetrating keratoplasty (26) and enucleation/evisceration (7) as the most common. Best-corrected visual acuity at the 1-month and 3-month mark showed significant and nonsignificant improvement from pregluing, respectively (Wilcoxon paired sample *t* test; $P=0.006$ and less than 0.001 at 1 and 3 months, respectively).

TABLE 3. *Univariate Analysis of Corneal Gluing Application Failure*

Variable	OR	95% CI	*P*
Female	0.489	0.223–1.072	0.074
Age	0.998	0.979–1.018	0.865
Systemic condition	0.778	0.351–1.772	0.535
Systemic autoimmune condition	0.347	0.074–1.63	0.18
Systemic immunosuppression	0.625	0.254–1.54	0.307
Ocular surface disease	0.276	0.114–0.667	0.004
Use of ophthalmic corticosteroid	0.57	0.256–1.266	1.67
Size of perforation (LARGE)	6.562	2.058–20.928	0.001
Perforation (vs. thinning)	1.056	0.495–2.225	0.887
Seidel positive	1.034	0.465–2.302	0.934
Peripheral location (vs. central)	0.51	0.229–1.689	0.351
Microbial etiology	2.218	1.03–4.775	0.042
Laceration	1.551	0.552–4.358	0.405
Single glue application (vs. multiple)	2.711	1.182–6.219	0.019
Anterior chamber shallow	1.458	0.654–3.252	0.357
Indirect application	4.648	1.274–16.954	0.02

TABLE 4. *Multivariate Analysis of Corneal Gluing Application Failure*

Variable	Adjusted OR	95% CI	*P*
Large size of thinning/perforation (vs. small)	10.249	2.11–49.781	0.004
Perforation (vs. thinning)	2.442	0.622–9.584	0.201
Peripheral location (vs. central)	1.45	0.268–7.86	0.666
Microbial etiology (vs. other)	1.259	0.319–4.962	0.742
Single corneal glue application (vs. multiple)	5.261	1.109–24.949	0.037

Within the cohort of patients receiving a nonenucleation/evisceration surgery within 1 month of initial glue application, significant improvement in vision was seen at 3 months compared with pregluing (Wilcoxon paired sample *t* test; $P=0.016$); within the cohort of patients not receiving surgery within 1 month of initial glue application, significant improvement in vision was observed at both 1 and 3 months compared with pregluing (Wilcoxon paired sample *t* test; $P=0.028$ and 0.007 at 1 and 3 months, respectively; Table 6).

DISCUSSION

Although tissue adhesives have not been approved by the Food and Drug Administration for ocular use, the use of corneal glue is standard treatment for the management of small or impending corneal perforations, including leaking blebs, descemetoceles, and progressive thinning. Our understanding of the various infectious, immune, and traumatic etiologies that lead to impending or frank corneal perforation has advanced significantly in recent decades, but the data guiding clinical decision-making for corneal gluing have lagged. This case series represents the second-largest study to date describing the clinical characteristics and outcomes of corneal gluing application.

Our study shows a corneal gluing application success rate of 53.1%, defined as an intact globe without need for subsequent intervention at 1 month after initial glue application. Success rates in the literature have varied significantly, ranging from 29% to 86% depending on various definitions of success.[11,13–18] Specifically, the need for subsequent surgical intervention is high: within 3 months of initial gluing, over 40% of eyes required definitive surgery. These data reinforce the concept that corneal gluing is a temporary intervention that necessitates close follow-up care.

Larger thinning/perforation size, single glue application, microbial etiology, indirect application via trephined sterile drape, and lack of ocular surface disorder were significantly associated with gluing failure at 1 month, whereas gender, age, systemic conditions, autoimmune conditions, systemic immunosuppression, ocular corticosteroid treatment, perforation (vs. thinning), Seidel positivity, location, and AC depth at gluing were features not associated with gluing failure at 1 month. Over time, patients who underwent multiple glue applications had improved globe stability, although this was nonsignificant. Identification of features associated with and, just as importantly, not associated with gluing failure can help clinicians make informed decisions when initially choosing between corneal glue versus other management techniques.

Notably, our data show that multiple glue applications are associated with a greater globe integrity compared with single glue application. This is important for clinicians who are contemplating surgery versus reglue after initial gluing failure. It should be noted that the OR of failure for single versus multiple corneal glue applications decreases over time, suggesting that advantage in globe integrity for multiple corneal glue applications diminishes with time but still persists. A similar trend was noted by Yinet al.[11] in their case series. Thus, an important element of care, especially in patients with glue reapplication after initial glue failure, should be close follow-up to ensure globe integrity.

In both univariate and multivariate analysis, larger size of thinning/perforation (>6 mm^2) was the most important factor linked to corneal gluing failure. Corneal gluing is indicated for thinning/perforations less than 3 mm^2, with our data suggesting greater than 6 mm^2 as a relative contraindication for corneal gluing. In cases where viable donor tissue is not immediately available for large perforations, gluing for these perforations is warranted but subsequent surgical intervention within days should be expected and planned. Interestingly, indirect application of corneal glue via sterile trephined drape was also associated with significantly greater rates of failure, although only 11 patients were administered corneal glue in this fashion. The benefit of indirect application is that glue may better adhere to the periphery of the perforation to seal the lesion. However, it is also possible that this is due to

TABLE 5. *Complications and Surgical Interventions Within 1 month of Corneal Glue Application*

Complication	37
Neovascularization	28
Stromal inflammation	5
Ocular hypertension/glaucoma	4
Surgical intervention	37
Penetrating keratoplasty	26
Enucleation/evisceration	7
Amniotic membrane transplant	1
Conjunctival flap	1
Patch graft	1
Tarsorrhaphy (complete)	1

TABLE 6. *Visual Acuity Outcomes in logMAR Before Gluing, at 1 month After Gluing, and 3 months After Gluing for Eyes That Underwent a Nonenucleation/evisceration Surgical Procedure Within 1 month (Surgery) and Eyes That did Not Undergo a Surgical Procedure Within 1 month*

	BCVA Preglue		BCVA 1 month		BCVA 3 months	
	No Surgery	Surgery	No Surgery	Surgery	No Surgery	Surgery
Number	87	29	85	27	87	26
Mean	1.991	2.208	1.856	1.956	1.763	1.774
SD	0.705	0.546	0.742	0.673	0.821	0.764
P value (compared with pregluing)			0.028*	0.102	0.007*	0.016*

*Indicates statistically significant ($p < 0.05$).

Paired sample *t* test (Wilcoxon) was performed to compare visual acuity differences at 1 and 3 months with pregluing.

BCVA, best-corrected visual acuity.

a selection bias as indirect application may be chosen by clinicians when tissue is more friable. Larger datasets are needed to compare direct and indirect corneal gluing application methods.

The proportion of thinning/perforations because of microbial etiology was relatively high at 45.3%, with previous studies reporting rates of 20% to 49%.[11,13–15,19] Several studies have shown CTA to have an inherent bacteriostatic effect, suggesting an advantage of their use in microbial cases.[9,16] However, our data showed that microbial etiology was associated with corneal gluing failure; 75.9% of eyes with microbial etiology required surgery compared with a surgery rate of only 44.3% for noninfectious causes. Although the bacteriostatic properties of CTA are well established, there is no evidence supporting the bactericidal properties of CTA. This may explain why microbial etiology was associated with a higher glue failure rate in univariate analysis. Moreover, gluing may be used in the short run in microbial cases to improve the outcome of future surgical intervention, enabling enough time for antibiotics to sterilize the infiltrate in hopes of a better surgical outcome.

Several complications linked with CTA application have been reported, including corneal neovascularization, ocular hypertension, stromal inflammation, and endophthalmitis. The rate of complications in our study was nearly 30% at 1 month after glue application, with neovascularization as the most common. Previous case series[18] and experimental studies[20] indicate that corneal neovascularization is common after gluing and an anticipated reaction of the corneal healing process. How neovascularization after corneal gluing affects the outcome of subsequent surgery has not been studied. However, it is known that neovascularization increases the likelihood of penetrating keratoplasty rejection via introduction of immune cells into the immune-naïve cornea. Four and nine patients had ocular hypertension at 1 and 3 months, respectively. Ocular hypertension and glaucoma have been frequently reported in keratitis because of microbial cause. This may be due to inflammation causing neovascularization, fibrosis of the angle, or changes in the angle after keratoplasty.[21]

This study is not without limitations. First, this study was conducted in the context of a tertiary academic medical center with a significant patient population referred from nearby community eye centers or hospitals. As such, the patient presentation and care received may not be reflective of the general community. Different institutions may have a varied threshold for surgical intervention based on local surgeon training, donor corneal tissue availability, and accessibility of operating rooms. Second, this was a retrospective case series based on chart review, with inherent bias because of this methodology. Only one previous randomized controlled trial exists on corneal gluing outcomes, a 2003 study comparing fibrin glue with CTA in 41 eyes.[18] Third, patients meeting inclusion criteria were determined by the fidelity of current procedural terminology coding. Corneal gluing patients often presented in an emergency department setting, making coding errors possible because of charting errors in the high-intensity environment. In addition, although "success" is defined as the absence of the need for future surgical intervention in our study, there may be cases where what appears to be a failure is actually a clinical success. For example, using glue to stabilize the AC for planned surgery the next day would be considered a success despite the need for further intervention. However, this definition effectively captures many of the goals of corneal gluing and enables comparison of outcomes at our institution with those in existing literature. Finally, the added globe stability seen with repeated glue applications may be self-selecting, as tissue that may be more likely to heal is preferentially selected for repeat gluing versus surgical intervention.

Together, our data suggest that corneal gluing is an effective temporizing measure for the management of corneal thinning and perforations, but the need for subsequent surgical intervention is high. When faced with the decision to proceed to surgery after initial gluing failure, clinicians may consider additional glue applications, especially for smaller lesions. This can provide added stability to the globe, often buying additional time if there is clinical uncertainty about the need for surgery or limited donor tissue availability.

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