The Ocular Surface 18 (2020) 795–800

Contents lists available at ScienceDirect

The Ocular Surface

journal homepage: www.elsevier.com/locate/jtos

Original Research

# Efficacy of cyanoacrylate tissue adhesive in the management of corneal thinning and perforation due to microbial keratitis

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ARTICLE INFO

*Keywords:*
Cyanoacrylate
Tissue adhesive
Corneal glue
Corneal thinning
Corneal perforation
Infectious keratitis
Bacterial keratitis

ABSTRACT

*Purpose:* Report the efficacy of cyanoacrylate tissue adhesive (CTA) application in the management of corneal thinning and perforations associated with microbial keratitis.

*Methods:* A retrospective review of consecutive patients who underwent CTA application for corneal thinning and perforation secondary to microbiologically proven infectious keratitis between 2001 and 2018 at a single center. We defined successful CTA application as an intact globe without tectonic surgical intervention.

*Results:* The cohort included 67 patients, and 37 presented with corneal perforation while 30 had corneal thinning. The perforation/thinning was central/paracentral in 43 eyes and peripheral in 23 eyes. The underlying infectious etiologies were monomicrobial in 42 cases (35 bacterial, 3 fungal, 2 viral, and 2 acanthamoeba cases) and polymicrobial in 25 cases (22 polybacterial cases and 3 cases with a combination of Gram positive bacteria and fungus). The median duration of glue retention was 29 days. The CTA success rate was 73%, 64%, and 44% at 10, 30, and 180 days, respectively. CTA application appears more successful in monomicrobial (vs. polymicrobial) and Gram positive bacterial (vs. Gram negative) keratitis but the differences are statistically non-significant. The location of perforation/thinning and the use of topical corticosteroid were not associated with CTA failure.

*Conclusion:* CTA was moderately effective in restoring globe integrity in severe corneal thinning and perforation secondary to microbial keratitis in the short term. However the majority of patients require tectonic surgical intervention within 6 months. CTA application success is not significantly associated with the location of thinning/perforation or the use of topical corticosteroid.

## 1. Introduction

Microbial keratitis is a significant cause of monocular blindness across the world. Every year an estimated 1.5 to 2 million people lose their vision as a consequence of microbial keratitis across the globe [1]. In the United States, approximately 1 million patients visit health practitioners and 58,000 patients visit emergency departments for the treatment of microbial keratitis annually [2]. Severe stromal thinning in cases of microbial keratitis can result in significant ocular morbidity, and recalcitrant cases often result in corneal perforation. Such cases are considered an ophthalmic emergency and require urgent intervention to maintain globe integrity. Inadequate management of corneal perforation may result in catastrophic sequelae such as endophthalmitis, suprachoroidal hemorrhage, vision loss, and enucleation.

Cyanoacrylate was first discovered by Coover and colleagues in 1942, at Kodak Research Laboratories. In 1959, they reported the unique adhesive properties of the polymer and suggested its possible use for the closure of surgical incisions. Ever since, the application of Cyanoacrylate tissue adhesive (CTA) has become the initial treatment of choice for severe corneal thinning and perforation as a temporizing measure to provide tectonic strength to the affected corneal tissue. Before application, the esters of cyanoacrylate exist as monomers in a viscous liquid state. Upon application, the monomers are exposed to the anions from the tissue, which triggers the polymerization reaction and promotes its binding to the tissue. In 1968, Webster et al. first reported CTA application for the repair of a perforated corneal ulcer caused by Moraxella lacunata infection [3]. Since then, multiple reports have highlighted the efficacy of CTA application in treating corneal perforation including due to microbial keratitis [4–6]. However, the current literature lacks evidence comparing the efficacy of CTA application in management of keratitis cases caused by various etiologies. In this retrospective case series, we report the clinical characteristics and

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https://doi.org/10.1016/j.jtos.2020.08.001
Received 15 May 2020; Received in revised form 14 July 2020; Accepted 3 August 2020
Available online 19 August 2020

outcomes of CTA application in 67 eyes diagnosed with keratitis due to diverse causative organisms at the Cornea Service of the Massachusetts Eye and Ear, Boston between 2001 and 2018.

## 2. Methods

We obtained the approval of the Institutional Review Board/Ethics Committee at Massachusetts Eye and Ear for this study. The study was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and adhered to the tenants of the Declaration of Helsinki.

We performed a retrospective review of the clinical charts of consecutive patients who were treated for corneal perforation or thinning associated with infectious keratitis at the Cornea Service of Massachusetts Eye and Ear from January 2001 to January 2018.Consecutive subjects were identified from our electronic medical record database using the diagnostic (ICD) codes and current procedural terminology (CPT) codes. The indications for corneal CTA application were severe corneal thinning or perforation due to an active infectious etiology, which was microbiologically confirmed by the Gram stain of corneal scrapings, presence of bacterial, fungal, viral, or parasitic organisms in the culture, confocal microscopy of the cornea, and/or pathology of corneal tissues. Demographic information, medical history, ophthalmic history, systemic and ophthalmic medications, best-corrected distance visual acuity (BCVA), intraocular pressure (IOP) in patients with corneal thinning, causative organism(s), location and size of perforation/thinning, number of CTA applications, and subsequent interventions were recorded in the Research Electronic Data Capture Software (REDCap, Vanderbilt University, Nashville, TN). The location of thinning and perforation was reported and recorded in the medical records by the treating ophthalmologists. Where there was clear documentation of the location (i.e. distance from limbus or center), we followed the following guidelines: the central 2 mm diameter was defined as the central zone of the cornea, an outer diameter between 3 and 8 mm as the paracentral zone, and the 9–11 mm as the peripheral zone. Seven patients with a working diagnosis of infectious keratitis but without a microbiological confirmation were excluded from the study and patients with incomplete data records were excluded.

The application of CTA was performed by ophthalmology trainees or attending physicians at a slit lamp in the clinic or in a procedure/operating room under topical or peribulbar anesthesia per the treating physician's preference. A combination adhesive of 2-Octyl Cyanoacrylate and *n*-Butyl Cyanoacrylate (MSI-Epiderm Glue + Flex; Medislav Services Inc., Markham, ON, Canada) was used. At Mass Eye and Ear, the majority of physicians including trainees use the following glue technique: the corneal epithelium is debrided near the area of thinning/perforation, the area is dried with a surgical sponge, one drop of cyanoacrylate glue is placed onto a small circular sterile plastic drape, and the glue/drape patch is then applied to the area of thinning/perforation, followed by a bandage contact lens. CTA application was repeated in cases of hypotony, positive Seidel test, and shallow/flat anterior chamber. The decision regarding the reapplication of CTA and/or surgical intervention was determined by the treating ophthalmologist.

The BCVA data, which was measured using the Snellen chart, was converted to the logarithm of the minimum angle of resolution (LogMAR) chart for the statistical analysis [7,8]. However, we did not convert the visual acuities of light perception and no light perception. The continuous variables are reported as mean (±standard deviation) or median (with interquartile range), and categorical variables are reported in numbers (percentage). A successful CTA application was defined as an intact globe without tectonic surgical intervention (regardless of the number of CTA applications) and Kaplan-Meier curve of CTA application success was generated using Prism 8 Software for MacOSX v.X.5.3 (GraphPad Software Inc., La Jolla, CA). Since the corneal glue is a temporalizing measure to secure the globe and the majority of glue failure occurred within one month of application, we arbitrarily chose 1 month as a time-point of interest and performed Fisher's Exact Test to evaluate the correlation between different variables and success of CTA application at 1-month using Prism 8 Software. A value of $p < 0.05$ was considered statistically significant.

## 3. Results

The cohort included 67 patients with a median age of 67 years, and 39 (58%) were women. The detailed demographics and clinical characteristics of 67 eyes of 67 patients at presentation are recorded in Table 1. Amongst the patients, 58 (87%) had systemic condition(s), with hypertension being the most common (30, 45%), followed by autoimmune diseases (21, 31%) and hypercholesterolemia (15, 22%). Fourteen patients (21%) were prescribed systemic immunosuppressants, including oral corticosteroids (11, 16%) and non-steroidal immunosuppressive medications (5, 7%). Forty-six patients (69%) presented with ocular comorbidities including neurotrophic keratopathy (21 patients), eyelid disorders (19 patients), and dry eye disease (15 patients). At the time of CTA application, 63 patients (94%) were on anti-microbial therapy including antibiotics (62, 93%), anti-viral (13, 19%), anti-fungal (8, 12%) and anti-amoebic (2, 3%) medications; 48 patients (72%) were on topical or had been given subconjunctival corticosteroids and 27 patients (40%) were on glaucoma medications.

The clinical characteristics of perforation or severe corneal thinning secondary to infectious etiologies and subsequent CTA application are

**Table 1**
Demographic and Clinical Characteristics of 67 Patients and 67 Eyes at baseline.

| | | |
|---|---|---|
| Age, median (range) | | 67 (13–97) |
| Sex | Female (%) | 39 (58%) |
| | Male (%) | 28 (42%) |
| Patients with systemic conditions, n (%)[a] | | 58 (87%) |
| Hypertension | | 30 (45%) |
| Autoimmune disease | | 21 (31%) |
| Hypercholesterolemia | | 15 (22%) |
| Diabetes | | 15 (22%) |
| Thyroid disease | | 12 (18%) |
| Gastrointestinal disease | | 11 (16%) |
| Cardiovascular disease | | 10 (15%) |
| Use of systemic immunosuppression, n (%) | | 14 (21%) |
| oral corticosteroid | | 11 (16%) |
| non-steroidal immunosuppressive medications | | 5 (7%) |
| Laterality | | |
| Right eye (%) | | 38 (57%) |
| Left eye (%) | | 29 (43%) |
| Patients with ocular surface disease[b], n (%) | | 46 (69%) |
| Neurotrophic keratopathy | | 21 (31%) |
| Eye lid disorder | | 19 (28%) |
| Dry eye disease | | 15 (22%) |
| Use of ophthalmic medication, n (%) | | 67 (100%) |
| anti-microbial | | 63 (94%) |
| antibiotic | | 62 (93%) |
| anti-viral | | 13 (20%) |
| anti-fungal | | 8 (12%) |
| anti-amoeba | | 2 (3%) |
| corticosteroid | | 48 (72%) |
| topical | | 47 (70%) |
| subconjunctival | | 2 (3%) |
| glaucoma | | 27 (40%) |
| cycloplegic | | 23 (34%) |
| oral doxycycline | | 9 (13%) |
| NSAIDs | | 7 (10%) |
| cyclosporine | | 1 (2%) |
| Others | | 5 (8%) |

[a] Only systemic conditions present in 15% or more in the cohort are listed in the table.

[b] Ocular surface diseases present in 15% or more in the cohort are listed in the table.

reported in Table 2. Amongst the patients, 37 (55%) had a corneal perforation (diagnosed with a positive Seidel Test), and 30 (45%) had severe thinning of the cornea. The corneal perforation or thinning was central or paracentral in 43 eyes (64%) and peripheral in 23 (34%) eyes. The median size of the corneal perforation/thinning was 3.75 $mm^2$. The mean and median numbers of total CTA applications were 1.48 and 1, with 23 eyes (37%) requiring more than one application within one month of the initial application. The median BCVA (LogMAR) at the time of application and after CTA application was 3.0 and 3.6 [Snellen equivalent 20/20,000 (hand motion at 2 feet) and 20/80,000 (hand motion at face)], respectively. No iris prolapse was noted in any of the patients.

The underlying infectious etiologies leading to corneal perforation/thinning are listed in Fig. 1. Among 67 eyes, 42 cases were monomicrobial (35 bacterial, 3 fungal, 2 viral, and 2 acanthamoeba cases) and 25 were polymicrobial (22 polybacterial cases, and 3 cases with a combination of Gram positive bacteria and fungus). We then categorized the spectrum of microbial organisms in Table 3. Fifty-eight cases (87%) were confirmed by microbial culture. Amongst the organisms isolated in microbial culture, there were 32 Gram positive (most common staphylococcal species), 11 Gram negative (most common *Pseudomonas aeruginosa*), 4 fungal and 1 herpes simplex viral isolates. Nine patients were diagnosed using alternative diagnostic techniques including Gram staining, confocal microscopy, and pathology.

Within one month of CTA application, 21 patients (31%) required no further intervention, 20 patients (30%) required reapplication of CTA, and 18 patients (27%) required surgical intervention (Table 4). Among these 18 patients, 17 patients underwent penetrating keratoplasty, and 1 patient underwent keratoprosthesis implantation. The success of CTA application is shown in the Kaplan–Meier curve in Fig. 2. Success was defined as an intact globe without the need for tectonic surgical intervention regardless of the number of applications performed. The CTA success rate was 73% at ten days, 64% at 30 days, and 44% at 180 days. The mean and median duration of CTA retention was 141 days and 29 days, respectively. In our patient cohort, neovascularization (9, 13%), stromal infiltration (8, 12%) and inflammation (3, 5%) were observed after CTA application.

Since CTA application is a temporalizing measure to secure the globe and the majority of glue failure occurred within one month of application, we chose 1 month as a time-point of interest and analyzed factors that may be associated with CTA application failure at 1 month. There was no significant difference in CTA success rate between central/paracentral and peripheral lesions (63% vs 67%, $p = 0.791$), or between eyes with and without ocular surface disease (59% vs 61%, $p = 0.853$). CTA success rate was slightly lower in patients with polymicrobial keratitis compared to monomicrobial keratitis (50% vs. 65%), but the difference was not statistically significant ($p = 0.28$, Fig. 3A) The success rate was moderately higher in keratitis caused by Gram positive bacteria compared to Gram negative bacteria (70% vs. 53%) but the difference was not statistically significant ($p = 0.33$, Fig. 3B). Lastly, patients who were on ophthalmic corticosteroids had similar success rate compared to those who were not (61% vs 62%, $p > 0.99$, Fig. 3C).

**Table 2**
Clinical characteristics of corneal perforation/thinning and CTA application.

| | |
|---|---|
| Initial presentation, n (%) | |
| perforation | 37 (55%) |
| thinning | 30 (45%) |
| Location of perforation/thinning, n (%) | |
| central/paracentral | 43 (64%) |
| peripheral | 23 (34%) |
| Not recorded | 1 (1%) |
| Median size of perforation/thinning in $mm^2$ (IQR)[a] | 3.75 (1.33–14.03) |
| Number of CTA applications per eye | |
| Mean (SD) | 1.48 (0.73) |
| Median (IQR) | 1 (1–2) |
| Range | 1–4 |
| Median BCVA at time of CTA application in logMAR (IQR)[b] | 3.0 (2.00–3.60) |
| Range (Snellen) | 20/25 - NLP |
| Median IOP at time of CTA application in mmHg (IQR)[b] | 12.0 (10.0–15.5) |
| Range | 8–45 |
| Median BCVA after CTA application in logMAR (IQR)[b] | 3.6 (1.93–3.6) |
| Range (Snellen) | 20/25 - NLP |

CTA: cyanoacrylate tissue adhesive, IQR: interquartile range, SD: standard deviation.
BCVA: best corrected visual acuity, LogMAR: logarithm of the minimum angle of resolution.
IOP: intraocular pressure, NLP: no light perception.
[a] Size of perforation/thinning was recorded in 43 eyes.
[b] BCVA and IOP at time of CTA, and BCVA after CTA were recorded in 62, 30, and 56 eyes respectively.

## 4. Discussion

Our study, including 67 eyes, is the one of the largest retrospective case series reporting the efficacy of CTA in fungal, bacterial, viral, amoebic as well as polymicrobial infectious keratitis. The majority of these cases are due to bacterial etiologies. Our data demonstrate that patients often require more than one CTA application and the median retention of CTA is 29 days. CTA application is moderately successful in the short term but the majority of patients require tectonic procedures to maintain globe integrity within 6 months. CTA application appears to be more successful in eyes with monomicrobial (vs. polymicrobial) and in eyes with Gram positive (vs. Gram negative) bacterial keratitis. The location of thinning/perforation, the presence of ocular surface diseases, or the use of ophthalmic corticosteroid were not associated with glue failure.

We previously reported the efficacy of CTA application in treating corneal thinning and perforation related to all etiologies (infection, immune melt, chemical injury, and trauma) [4]. Compared to eyes glued for all causes, these glued for microbial keratitis-related corneal thinning and perforation had larger areas of perforation/thinning (3.75 $mm^2$ in infectious cases vs 3.1 in all etiologies) and worse vision (63.2% with vision of hand motion or worse in infectious cases vs 46.2% in all etiologies) at time of presentation. The duration of glue retention in eyes with microbial keratitis is half of that in eyes glued for all causes (29 vs 58 days). Interestingly we previously found an odds ratio of 1.68 in glue failure associated with immune-mediated sterile melt (as compared to other causes including infection). These results suggest that despite larger size of perforation/thinning, worse vision at presentation, and shorter retention of glue in microbial keratitis, CTA application may be more successful in temporizing thinning and perforation secondary to microbial keratitis, compared to that in non-infectious immune-mediated melt.

CTA have been reported to be effective in closing small wounds (<3 mm in diameter) [9]. CTA can avert corneal melts by blocking the migration of polymorphonuclear leukocytes to the site of injury as well as by antagonizing collagenases locally [10]. Moreover, the results from published *in vitro* and a few *in vivo* studies report the unique antimicrobial activity of CTA, attributed to formaldehyde, which is the primary by-product of hydrolytic degradation during polymerization. Formaldehyde has known antimicrobial properties via alkylation of chemical groups in proteins and nucleic acids of the infective organisms [11].

Jandinski and Sonis first reported the *in vitro* inhibitory effects of isobutyl cyanoacrylate on Streptococci, Neisseria catarrhalis, Aerococcus viridans, and *Staphylococcus aureus* [12]. A similar bacteriostatic activity of butyl-cyanoacrylate was observed by Eiferman and colleagues [13]. Short chain ethyl esters of cyanoacetate have been shown to be selectively effective against *Escherichia coli* and Escherichia faecalis whereas octyl cyanoacrylate has been shown to have intrinsic

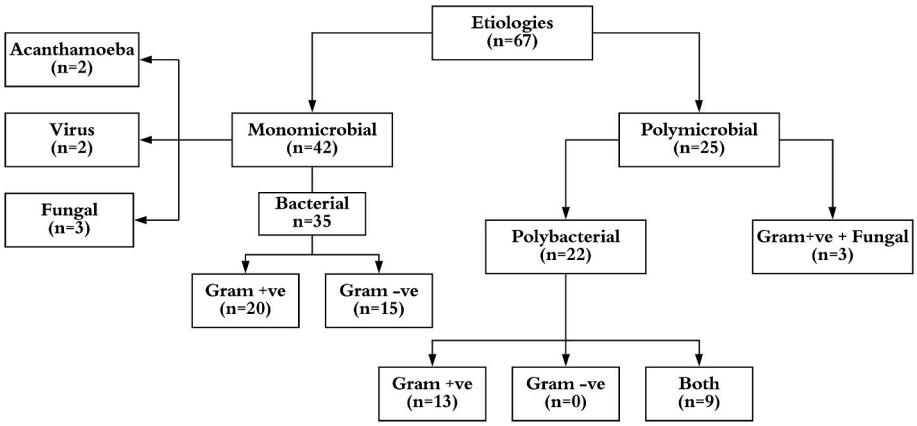


**Fig. 1.** The underlying etiologies leading to corneal thinning and/or perforation requiring CTA application.

**Table 3**
Spectrum of organisms isolated from corneal tissue of 67 eyes.

| | | |
|---|---|---|
| Culture | | |
| Positive | | 58 (87%) |
| Negative | | 9 (13%) |
| Organisms isolated by culture | | |
| Bacteria | | |
| Gram positive | | |
| | Staphylococcus species | 32 |
| | • *Staphylococcus aureus* | 13 |
| | • Staphylococcus epidermidis | 2 |
| | • Unspecified | 17 |
| | Streptococcus species | 12 |
| | Diphtheroids | 11 |
| | Corynebacterium diphtheriae | 1 |
| | Gemella morbillorum | 1 |
| | Propionibacterium acnes | 1 |
| Gram negative | | |
| | *Pseudomonas aeruginosa* | 11 |
| | Serratia species | 3 |
| | Achromobacter xylosoxidans | 1 |
| | Citrobacter koseri | 1 |
| | Haemophilus influenzae | 1 |
| | Moraxella species | 1 |
| | Stenotrophomonas maltophilia | 1 |
| Fungus | | |
| | Candida | 1 |
| | Unspecified | 3 |
| Virus | | |
| | Herpes Simplex Virus | 1 |
| Organisms isolated by other techniques (culture-negative) | | |
| Pathology positive[a] | | 3 |
| Gram stain[b] | | |
| | Gram Positive | 2 |
| | Gram Negative | 4 |
| Confocal microscopy[c] | | 2 |

[a] Pathological analysis was used in two cases of fungal keratitis and one case of HSV keratitis.
[b] Gram staining showed the presence of both Gram-positive and Gram-negative bacteria in two patients.
[c] Confocal microscopy was used in the diagnosis of two cases of Acanthamoeba keratitis.

**Table 4**
Outcomes of CTA application and surgical interventions after initial application.

| | |
|---|---|
| **CTA Application** | |
| Total eyes glued | 67 |
| Lost to follow up | 8 (12%) |
| At 1 month follow up | |
| No intervention | 21 (31%) |
| Additional CTA application | 20 (30%) |
| Surgical intervention | 18 (27%) |
| **Surgical interventions** | |
| Penetrating keratoplasty | 17 (25%) |
| Keratoprosthesis | 1 (2%) |

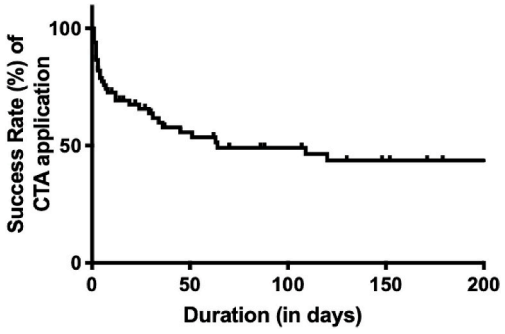


**Fig. 2.** Outcomes of CTA application. Kaplan–Meier curve for CTA application success. Success is defined as an intact globe without tectonic surgical intervention.

anti-microbial activity against Gram-positive and non-pseudomonas Gram-negative bacteria [14–16]. Outcomes from our study found a moderately higher efficacy of CTA in Gram-positive (70%) compared to Gram-negative keratitis (53%). A moderately lower efficacy of CTA in Gram-negative keratitis has been attributed to the outer lipopolysaccharide capsule surrounding the cell wall, reducing the penetration of the glue. The shorter chain derivates of cyanoacrylate can cause a severe inflammatory response to the area of application, whereas the longer-chain-derivates of cyanoacetate have a reduced anti-microbial activity as well as less toxicity to the corneal tissue due to less generation of by-products [15,17]. However, post-polymerization, the cyanoacrylate monomers become inert and are known to lose their antimicrobial properties within an hour of the application after polymerization; on the contrary, the opacification of CTA upon polymerization makes it challenging for the ophthalmologists to diagnose recurrent or new concomitant infections [18–20]. In our cohort, more than one third of the cases with Gram positive keratitis had a polymicrobial infection, which may have affected the efficacy of CTA in these patients. Our analyses also revealed that CTA success rate was moderately lower in patients with polymicrobial (50%) keratitis compared to monomicrobial keratitis (65%).

Moorthy et al. reported a 62.5% CTA failure rate in patients with herpes simplex virus keratitis even when patients were prescribed

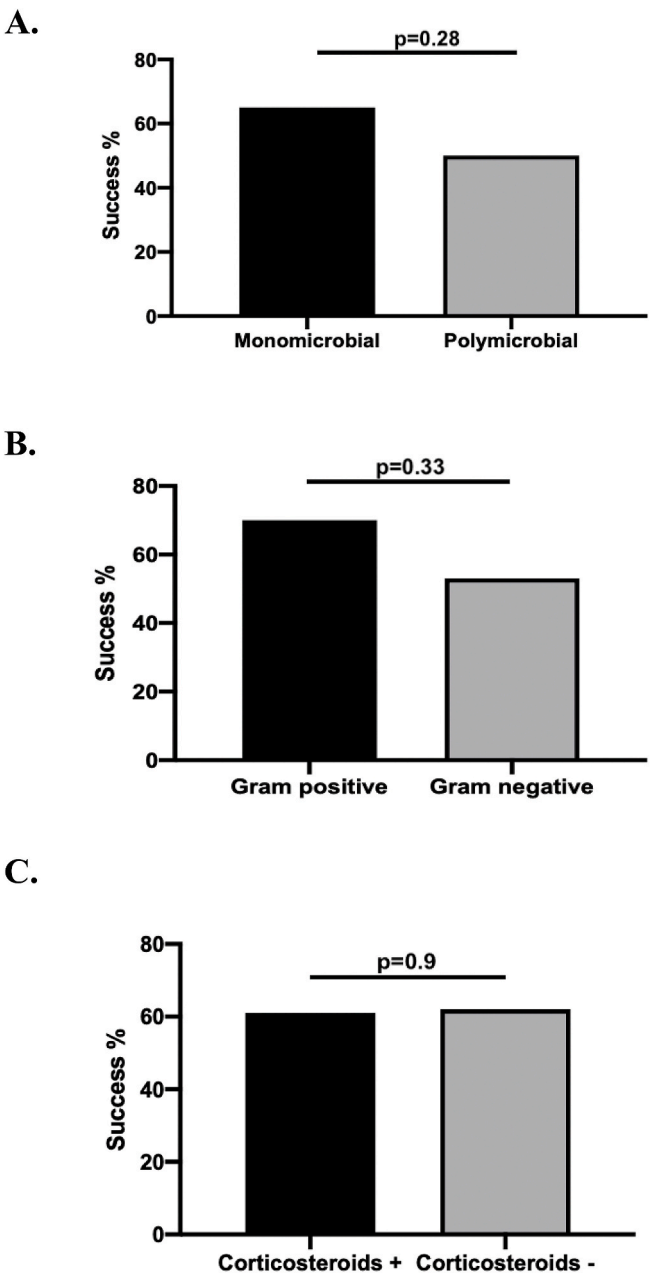


**Fig. 3. Identification of factors associated with CTA success at 1 month.** (A) Monomicrobial vs. Polymicrobial (B) Gram positive vs. Gram negative bacteria (C) Use of ophthalmic corticosteroid vs. No corticosteroid.

acyclovir prophylaxis. The rate of failure was higher in patients without any antiviral prophylaxis [5]. Garg and colleagues reported high efficacy of *n*-butyl cyanoacrylate against keratomycosis-related thinning or perforation. In their study, 64% of the cases resolved in scar formation, while an additional 12% maintained the structural integrity of the globe [21]. These results were recently confirmed by Dogan et al. in an *in vitro* study, where they tested the anti-fungal activity of 2-butyl cyanoacrylate and reported a high antimicrobial action against all species of yeast and mold except Aspergillus flavus, Aspergillus oryzae, Chrysosporium sp. and Phoma glomerate [22]. Of note, we use a combination of butyl and octyl esters of cyanoacrylate, which in theory provide coverage against polymicrobial corneal infections.

Our series shows that CTA application is moderately successful in the short term (within 30 days of application), although nearly one third of these patients required more than 1 CTA application. Approximately half of patients needed tectonic surgical intervention within 180 days of initial CTA application. Interestingly, there are seven cases where the glue patch was removed during follow-up and the duration between glue application and removal range from 14 to 317 days with a median of 70 days. Spontaneous loosening and/or dislodging of the glue patch was noted in the majority of these cases. These findings highlight the necessity of high clinical suspicion and regular follow-up to monitor the impending perforation of thinned out corneal tissue after CTA application. When CTA alone cannot provide adequate tectonic strength to the corneal tissue, it is combined with a drape patch, suture, or gas permeable contact lenses [23–25]. Other than CTA, fibrin glue is another widely used tissue adhesive as a temporizing measure to maintain the globe's integrity. In their *in vitro* studies, Chen et al. reported an absence of bacteriostatic activity by fibrin as compared to methoxypropyl cyanoacrylate and *n*-butyl cyanoacrylate [26].

Our study is limited by its retrospective nature. For instance, corneal stromal inflammation and infiltrates were reported after CTA application, but the authors were unable to differentiate whether these terms represented a sterile or still infectious case. In addition, our study has very few cases of viral keratitis and keratomycosis; therefore, a comparative analysis of the success of CTA between bacterial and non-bacterial cases cannot be performed. Since our practice is an academic tertiary eye care referral center, the cases reported here, as well as the treatment provided, may not be a true reflection of that seen in the community. Lastly, although our cohort has relatively large number of subjects compared to some of the previous studies, the number is still inadequate to demonstrate the statistical difference of certain analyses or to identify all relevant risk factors associated with CTA application failure using a multivariate regression analysis.

In summary, our data demonstrate that CTA application is effective in restoring globe integrity to the eye in cases of corneal thinning and perforation due to infectious keratitis in the short term and multiple applications are often required. Our study suggests that these patients should be monitored closely for re-perforation and the need for tectonic surgical intervention. CTA application appears more successful in monomicrobial (vs. polymicrobial) and Gram positive bacterial (vs. Gram negative) keratitis. The use of topical corticosteroid and location of perforation/thinning are not associated with CTA failure.

## Funding support

This study was supported by the National Eye Institute/National Institutes of Health Grant 5K12EY016335 to JY (trainee).

## Declaration of competing interestCOI

The authors declare no financial conflicts of interest.

## Author contributions

R.B.S., J.Y. and R.D. designed the study; R.B.S., A.Y., and S.Z. acquired data; R.B.S., S.Z. and J.Y. analyzed the data; R.B.S., A.Y. and J.Y. prepared the manuscript; R.B.S., T.H.D., J.Y. revised the manuscript; J. Y. and R.D. supervised the study; all authors read and approved the final manuscript.

## Acknowledgements

We would like to thank Dr. Man Yu and Dr. Rani Al-Karmi, for their assistance in the study.

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