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Outcomes of Cyanoacrylate Tissue Adhesive Application in Corneal Thinning and Perforation

Jia Yin, Rohan Bir Singh, Rani Al Karmi, Ann Yung, Man Yu, and Reza Dana

Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA 02114

Abstract

Aims: To report the outcomes of cyanoacrylate tissue adhesive (CTA) application in corneal thinning and perforation.

Methods: A retrospective interventional case series of 137 patients receiving CTA for corneal thinning and perforation in 140 eyes between 2001 and 2018 at a single-center was reviewed. Success rate and factors associated with glue failure were analyzed.

Results: Median age of the cohort was 63 years and 69 (50%) were female. One hundred fifteen patients (84%) had at least one systemic condition, 46 (34%) had autoimmune diseases. Eighty-nine eyes (64%) presented with perforation while 51 (36%) with thinning. The perforation/thinning was central/paracentral in 82 eyes (59%) and peripheral in 57 eyes (41%). Median size of perforation was 3.1 mm². Causes of perforation and thinning were microbial infection in 75 (55%), sterile melt in 49 (35%), laceration in 10 and keratoprosthesis melt in 8 eyes. Median glue retention was 58 days. Success rate of glue application (defined as intact globe without surgical intervention) was 72%, 61% and 46% at 10, 30 and 90 days post-glue application, respectively. Larger size of perforation/thinning, perforation (vs. thinning) and single glue application (vs. multiple) were correlated with higher failure rate. Systemic conditions, use of topical corticosteroid, etiologies and location of perforation/thinning were not significantly correlated with glue failure.

Conclusions: CTA application was moderately effective in stabilizing corneal perforation and thinning in the very short-term. Multiple applications are often required. Maintenance of globe integrity after glue application decreases with time and the need for surgical intervention remains high.

Keywords

cyanoacrylate; tissue adhesive; corneal glue; corneal thinning; corneal perforation; descemetocoele

INTRODUCTION:

Corneal perforation and severe thinning of the stroma (descemetocoele), caused by infectious, immune, and traumatic disorders, are ophthalmic emergencies that require prompt

intervention to retain ocular integrity and visual function. A delay in treatment may result in endophthalmitis, loss of vision and even loss of the eye. Current management includes placement of bandage contact lens, application of tissue adhesives, and surgical intervention such as amniotic membrane transplantation, corneal patch graft or transplantation. [1–3]

Cyanoacrylate tissue adhesive (CTA) combines cyanoacetate and formaldehyde, and polymerizes upon contact with fluid providing tectonic strength. [4] The United States Food and Drug Administration approved CTA for topical skin approximation in 1998. [5] Its use in corneal perforation was first reported in 1968 and it is now a first-line, albeit off-label, treatment for corneal perforation, especially when grafting is not feasible or immediately necessary. [4, 6, 7] Previous studies have reported various success rates of CTA in sealing perforation acutely [8–12], but the retention of CTA and maintenance of globe integrity over time has not been thoroughly examined. In addition, factors associated with glue failure have not been systematically analyzed. In this study, we review the use of CTA in 140 eyes with corneal perforation and thinning at the Massachusetts Eye and Ear Infirmary, Boston between 2001 and 2018, and report the clinical characteristics and outcomes.

METHODS:

We performed a retrospective review of clinical charts of all patients treated with CTA for corneal perforation or thinning at the Massachusetts Eye and Ear Infirmary, Boston, MA between January 2001 and January 2018. Institutional Review Board/Ethics Committee approval was obtained and the described research adhered to the tenets of the Declaration of Helsinki.

Subjects were identified with Current Procedural Terminology and diagnosis codes and electronic and paper medical records were reviewed. Cases with incomplete data or follow-up shorter than one week were excluded. The following data were collected in Research Electronic Data Capture (REDCap, Vanderbilt) by two authors (R.B.S and A.Y.): Demographic information, past medical and surgical histories, detailed ophthalmic history, systemic and ophthalmic medications, ophthalmic comorbidities, best-corrected distance visual acuity (BCVA), intraocular pressure (IOP), ocular examination, etiology, location and size of the perforation/thinning, total number of CTA applications, subsequent medical and surgical treatments, and the final outcome. The data were then independently verified by a third author (J.Y.). A combination adhesive of 2-Octyl Cyanoacrylate and n-Butyl Cyanoacrylate (MSI-Epiderm Glue+Flex; Medislab Inc., Canada) was used and it was applied per the treating ophthalmologist's preference. CTA was re-applied when the globe was no longer intact (judged clinically by positive Seidel test, hypotony, and/or shallow anterior chamber). Subsequent follow-up, re-application of CTA, medical, and surgical interventions were decided by the treating physician(s).

Statistical analysis

Visual acuity was converted from Snellen chart to logarithm of the minimum angle of resolution (LogMAR) as previously described.[13] Visual acuity of light perception and no light perception were not converted. Continuous variables were reported as mean (Standard

Deviation, SD) or median (interquartile range, IQR) and categorical variables were reported in numbers (percentage).

Survival analysis of glue application success

GraphPad Prism software version 5.00 for Windows was used for Kaplan Meier curve survival analysis (GraphPad Software, La Jolla California USA). Both the success of a single (initial) CTA application and multiple CTA applications were analyzed. In the case of a single CTA application, success is defined as an intact globe without additional intervention. Each eye was considered one sample (N=140) and subsequent glue application and surgical intervention were counted as 'events'. Repeat application was counted as a single event regardless of the times performed. In the case of multiple applications, success of multiple CTA application is defined as an intact globe without surgical intervention. Each eye was considered one sample (N=140) and subsequent surgical interventions were counted as 'events'.

Logistic regression analysis

To assess factors correlated with CTA failure, logistic regression was generated using SAS software 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). CTA failure was defined as open globe in need of surgical intervention within one month of the initial CTA applications (regardless of total number of CTA applied). Univariable analyses were performed using the following variables: age, sex, systemic conditions, systemic autoimmune conditions, use of systemic immunosuppression, significant ocular surface diseases (OSD), use of ophthalmic steroids, location, size, and etiologies of perforation/thinning, and total number of CTA applied. No mathematical transformation of variables was performed. In the final multivariable regression model, perforation (vs. thinning), location, use of topical steroid, sterile melt (vs. other causes) and single CTA application (vs. multiple) were included based on clinical relevance and to prevent overfitting of the model. Two-sided P value <0.05 was considered statistically significant.

RESULTS

A total of 137 patients were included in the study with a median age of 63 years and 69 (50%) were female. Baseline characteristics are shown in Table 1. Systemic conditions were present in 115 patients (84%). Hypertension was the most common systemic condition (54 subjects), followed by autoimmune diseases (46 subjects) including rheumatoid arthritis (RA), systemic lupus erythematosus, scleroderma, polymyalgia rheumatica, and granulomatosis with polyangiitis. Twenty-eight patients (20%) were on systemic immunosuppression including corticosteroids and/or steroid-sparing agents at time of presentation. Three patients had bilateral perforation or thinning that required bilateral CTA application, one case of RA-associated peripheral ulcerative keratitis, one case of severe alkali burn, and one case of biopsy-proven mucous membrane pemphigoid. Baseline characteristics of the 140 glued eyes are shown in Table 1. One hundred three cases (74%) had documented ocular surface diseases with eyelid disorder (41), neurotrophic keratopathy (41), and dry eye disease (34) being the most common. The majority of patients (129, 92%) were on topical anti-microbial treatment and 98 patients (70%) were on topical

corticosteroid at time of CTA application. Forty-seven patients (34%) were on glaucoma mediations.

The clinical characteristics of perforation/thinning and CTA application are shown in Table 2. Eighty-nine eyes (64%) presented with perforation (Seidel positivity), while 51 (36%) with severe thinning. The location was central or paracentral in 82 eyes (59%) and peripheral in 57 (41%). Median size of perforation was 3.1mm². Causes of perforation or thinning included microbial infection, RA-associated melt, graft-versus-host disease (GVHD)-associated melt, other non-infectious melts, laceration or mechanical trauma, keratoprosthesis melts, and burn; several cases are multifactorial. Sixty-seven of the 77 microbial cases (85%) were confirmed by gram stain, microbial culture, confocal microscopy, or pathology. The median and mean numbers of total CTA applications were 1 and 1.6 with 88 eyes (62.9%) requiring with more than one application. Median BCVA before and after CTA application was 2.3 and 2.0 in logMAR (P= 0.44, Wilcoxon matched pairs test, Supplementary data eFigure1).

The Kaplan-Meier curve of CTA success with single and multiple applications is shown in Figure 1. Success was defined as an intact globe without additional intervention (repeat glue application or surgery) in the case of single CTA application, and without surgical intervention in the case of multiple CTA application. The success rate of single and multiple CTA applications was 55% and 72% at 10 days, 39% and 61% at 30 days, and 28% and 46% at 90 days, respectively. The median retention of CTA was 58 days. Logistic regression was performed to identify factors associated with CTA failure (defined as open globe in need of surgical intervention within one month of initial CTA application). In univariable analysis (Supplementary data eTable1), while age, sex, systemic conditions, OSD, microbial etiology, laceration, keratoprosthesis, and history of corneal grafting were not significantly correlated with CTA failure; size of perforation/thinning (Supplementary data eFigure2) and single application were correlated with higher failure rate. The final multivariable model is shown in Table 3. Single application (vs. multiple) was significantly correlated with higher failure rate (odds ratio 3.09, P=0.01). Perforation (vs. thinning) was associated with higher failure rate (odds ratio 2.18) but statistically non-significant (P=0.06). The etiologies and location of perforation/thinning, and the use of topical corticosteroid were not significantly associated with glue failure.

Within one month of CTA application, complications associated with CTA such as corneal neovascularization and stromal inflammation were present in 17 and 15 eyes, respectively, out of 61 eyes with recorded CTA details (Table 4). The most common surgical intervention (Table 4) was penetrating keratoplasty (43 out of 52 eyes), followed by keratoprosthesis (5), enucleation/evisceration (3), and amniotic membrane transplant (1). No lamellar keratoplasty was performed in this cohort.

DISCUSSION

It has been 50 years since Webster *et al* first reported the use of CTA in sealing corneal perforation clinically.[6] Despite CTA's widespread use as a first-line treatment for corneal perforation and several previous reports on its success in sealing the globe acutely [8, 10,

11], the retention of CTA and maintenance of globe integrity over time, as well as factors associated with glue failure have not been systematically analyzed. The current study of 140 eyes, to our knowledge, is the largest case series reporting the outcomes of CTA application and the first to identify clinical characteristics associated with glue failure. The majority of patients (84%) presented with systemic conditions; one third had autoimmune diseases and 20% were on a systemic immunosuppressive regimen. Ophthalmic morbidities were prevalent (74%), and the overwhelming majority were on topical anti-microbial and corticosteroid treatments. A single CTA application was successful in restoring globe integrity in approximately half of the eyes at 10 days post-application, but nearly two-thirds of the cases required a secondary procedure such as re-application of CTA or surgery within 30 days. Multiple CTA applications improved globe stability compared to a single application, but the maintenance of intact globe declined with time. Perforation (vs. thinning), large size of perforation/thinning, and single application (vs. multiple) were associated with CTA failure; in contrast, sex, age, autoimmune conditions, use of topical steroids, location and etiologies of perforation/thinning were not significantly correlated with CTA failure.

Corneal melting and subsequent perforation are the end results of many ocular surface disorders, including infectious, immune, and traumatic etiologies. [3] Several earlier studies have examined these causes and the use of CTA (see Supplementary data eTable 2 for a brief summary of previous studies on the use of CTA in corneal thinning and perforation). [8, 11, 14] Our collective understanding of these conditions and treatments have improved significantly in the past thirty years, warranting an updated assessment of the non-surgical management of corneal perforation. [15–19] All but 5 cases in our series were between 2008 and 2018, representative of current population and practice. In our series, approximately half of the eyes received CTA application due to infectious keratitis, predominantly bacterial ulcers (49% of 140 eyes). CTA application due to bacterial infection in our series is higher than previously reported (range 20–29%, supplementary online data). [8, 10, 11, 14] On the other hand, we have lower rate of perforation/thinning associated with rheumatoid arthritis (10%) compared to previously reported (15–48%). [8, 10, 14] We speculate that more widespread and earlier use of disease-modifying antirheumatic drugs (DMARDs) in rheumatoid diseases may account for the differences. Our series also examined ocular surface comorbidities and found 75% of subjects presented with significant OSD, with lid abnormality and associated exposure, neurotrophic keratopathy, and dry eye disease most common. This reinforces the critical values of adequately managing these comorbidities to prevent corneal melt and perforation.

The success of CTA application in sealing corneal perforation varied significantly across studies (success rate of 29–86%), depending on the etiologies of perforation, indications for application, and definition of success. [8–12, 20] Our series demonstrate that multiple applications of CTA are often required, suggesting that failure to seal perforation after one application need not necessarily be interpreted as a requirement to proceed with surgery and that repeat glue attempts may be made. More importantly our study followed the maintenance of globe integrity post-glue application and showed a gradual decline over time. For instance, the success rate decreased from 72% at 10 days post-glue application, to 61% and 46% at 30 and 90 days, respectively. This reinforces the importance of close

monitoring and high clinical vigilance after CTA application. While the 're-glue' rate was higher in our series (63%) compared to previous studies, the retention of CTA was similar with a median duration of 58 days. [8–12, 14, 20] The longest duration of CTA in our series was 2016 days (about 5.5 years), slightly longer than a previous report. [21] One eye with significant lagophthalmos and exposure after severe facial alkali burn underwent a total of 11 CTA applications within 5 months and achieved a final BCVA of 20/25 without surgical intervention.

Complications associated with CTA have been reported including increased ocular surface inflammation, corneal neovascularization, and giant papillary conjunctivitis. [20, 22, 23] Although various forms of cyanoacrylate have been shown to inhibit gram-positive bacteria growth *in vitro* [24, 25], infiltrates could develop underneath the glue. The opacity of CTA makes diagnosing these new or recurrent infections more challenging and requires high clinical suspicion. [8, 14, 26] Our cohort demonstrated cases of persistent neovascularization and stromal inflammation after CTA application; however, it was not clear if the stromal inflammation in these cases was infectious or sterile based on clinical documentation. CTA can be applied directly from an applicator or syringe, or indirectly on a trephined sterile drape. [27] When CTA alone is insufficient to seal the wound, combination with suture, tectonic drape patch, paper, or rigid gas permeable contact lens have been reported to secure the globe. [28–30] In our recent experience, we have observed additional stability and security by placing a second contact lens, which likely decreases the movement of the underlying contact lens and subjacent CTA with blinking. Since CTA is non-biodegradable, potentially toxic and pro-inflammatory, use of alternative tissue adhesives in sealing corneal perforation and thinning has been explored. In a randomized controlled trial (RCT) by Sharma *et al*, fibrin glue showed similar efficacy in sealing perforation up to 3mm in diameter with fewer side effects compared to CTA. [20] Although fibrin glue is biocompatible and widely used in ocular surface surgery, it is designed for adhering soft tissue to one another, and not for filling in stromal defects or for applying to wet surfaces. In addition, fibrin glue takes longer to form plugs, lacks bacteriostatic property and has much lower bursting pressure compared to CTA. [25] New ways to restore corneal stroma and close corneal wounds include bioengineered collagen-based materials and synthetic polyethylene glycol derivatives. [4, 7, 31] Their clinical use in corneal perforation and thinning is subject of extensive ongoing investigation.

We performed regression analysis to identify factors associated CTA failure. While large wounds and single (vs. multiple) application are significantly associated with failure in both univariable (supplementary online data) and multivariable analyses; perforation (vs. thinning) is associated with failure but statistically non-significant ($P=0.06$). Of note, autoimmune conditions, existing OSD, the use of systemic immunosuppression, the use of topical corticosteroids, etiologies and the location of perforation are not significantly associated with CTA failure. Garg *et al* have reported a high success rate of 76% using CTA in fungal keratitis-related perforation [12], while Moorthy *et al* noted a much lower success rate of 37% in herpetic keratitis-related perforations. [9] Our study has too few cases of fungal and herpetic infections to compare to these series. We examined infectious etiology, trauma, keratoprosthesis, and corneal graft as potential factors in CTA failure, and found no

correlations in all analyses. In the multivariable analysis, immune-mediated sterile melt had an odds ratio of 1.68 for CTA failure, but this was not statistically significant.

The current study has several limitations. First, the study is retrospective and non-comparative in nature with inherent bias. To our knowledge, the aforementioned study by Garg *et al* comparing fibrin glue and CTA is the only RCT examining CTA. [20] Future studies comparing CTA with new generation of ophthalmic tissue adhesives are warranted. Second, our practice is an academic tertiary eye care referral center and the care may not be truly reflective of these seen in the community. Lastly, donor tissue and operating room availability is rarely a limiting factor in our practice; hence, the decision to intervene surgically at our center may differ from community practices.

In the aggregate, our data demonstrate that multiple CTA applications are often required to securely seal corneal perforation. Although cyanoacrylate glue is moderately successful in the very short term, the maintenance of globe integrity decreases with time; thus, the need for surgical intervention remains high. Our study suggests that eyes that have had cyanoacrylate glue application should be monitored closely, and repeat glue application needs to be considered before proceeding to surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Outcomes of CTA application. A. Kaplan-Meier curve of single CTA application success. Success is defined as an intact globe without additional intervention. B. Kaplan-Meier curve of Multiple CTA application success. Success of multiple CTA application is defined as an intact globe without surgical intervention.

CTA: cyanoacrylate tissue adhesive

Table 1.

Demographic and clinical characteristics of 137 subjects and 140 eyes at baseline

Age, median (range)	63 (13–97)
Sex	
Female (%)	69 (50.4%)
Male (%)	68 (49.6%)
Presence of systemic condition, No. (%) ^a	115 (83.9%)
Hypertension	54 (39.4%)
Autoimmune disease	46 (33.5%)
Non-Sjogren	28 (20.4%)
Sjogren	18 (13.1%)
Cancer	23 (16.8%)
Diabetes	22 (16.1%)
Thyroid disease	22 (16.1%)
Use of systemic immunosuppression, No. (%)	28 (20.4%)
oral corticosteroid	22 (16.1%)
non-steroidal immunosuppressive	9 (6.6%)
Laterality (140 eyes)	
Right eye No. (%)	65 (46.4%)
Left eye No. (%)	75 (53.6%)
Presence of ocular surface disease, No. (%)	103 (73.6%)
Eye lid disorder	41 (29.3%)
Neurotrophic keratopathy	41 (29.3%)
Dry eye disease	34 (24.3%)
SJS/TEN/MMP	10 (7.2%)
Chemical or thermal burn	4 (2.9%)
Ocular GVHD	6 (4.3%)
Others	23 (16.4%)
Use of ophthalmic medication, No. (%)	
Corticosteroid	99 (70.7%)
topical	98 (70.0%)
subconjunctival	4 (2.9%)
Anti-microbial	129 (92.1%)
antibiotic	127 (90.7%)
anti-viral	25 (17.9%)
anti-fungal	13 (9.3%)
anti-amoebea	4 (2.9%)
Anti-glaucoma	47 (33.6%)
Cycloplegic	39 (27.9%)
Oral doxycycline	19 (13.6%)
NSAIDs	9 (6.4%)
Restasis	7 (5.0%)
Others	12 (8.5%)

^aSystemic conditions with higher than 15% prevalence in the population are shown

SJS: Stevens-Johnson syndrome

TEN: toxic epidermal necrolysis

MMP: mucous membrane pemphigoid

GVHD: graft-versus-host disease

NSAIDs: nonsteroidal anti-inflammatory drugs

Table 2.

Clinical characteristics of corneal perforation/thinning and CTA application

Initial presentation	
perforation	89 (63.6%)
thinning	51 (36.4%)
Location of perforation/thinning	
central/paracentral	82 (58.6%)
peripheral	57 (40.7%)
unspecified	1 (0.7%)
Median size of perforation/thinning in mm ² (IQR) ^a	3.14 (1.25–9.00)
Causes of perforation or thinning, No. (%)	
Microbial	77 (55.0%)
Bacterial	69 (49.3%)
Viral	4 (2.9%)
Fungal	7 (5.0%)
Acanthamoeba	2 (1.4%)
Sterile melt (non-infectious)	49 (35.0%)
Rheumatoid associated	15 (10.7%)
GVHD	3 (2.1%)
Others	31 (22.1%)
Laceration	10 (7.1%)
Keratoprosthesis melt and extrusion	8 (5.7%)
Burn (Alkali, acid and electrical)	4 (2.9%)
Total number of CTA application per eye	
Mean (SD)	1.6 (1.2)
Median (IQR)	1.0 (1.0–2.0)
Range	1 – 11
Median BCVA at time of CTA application in logMAR (IQR) ^b	2.3 (0.7–3.6)
Range	20/20 - NLP
Median IOP at time of CTA application in mmHg (IQR) ^b	13.0 (10.0–15.0)
Range	5–45
Median BCVA after CTA application in logMAR (IQR) ^b	2.0 (1.0–3.6)
Range	20/15- NLP

^aSize of perforation/thinning was recorded in 77 eyes^bBCVA and IOP at time of CTA, and BCVA after CTA were recorded in 119, 64, and 112 eyes respectively

CTA: cyanoacrylate tissue adhesive

IQR: interquartile range

GVHD: graft-versus-host disease

SD: standard deviation

BCVA: best corrected visual acuity

LogMAR: logarithm of the minimum angle of resolution

IOP: intraocular pressure

NLP: no light perception

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Table 3.

Multivariable regression analysis of CTA application failure, defined as an open globe in need of surgical intervention within one month of the initial CTA applications (regardless of total number of CTA applied). C statistics 0.673.

Variable	Unadjusted odds ratio	Multivariable analysis		
		Odds ratio	95% CI	P value
Perforation (versus thinning)	1.71	2.18	0.95 – 4.97	0.06
Central location (versus peripheral)	1.05	1.21	0.53 – 2.74	0.66
Use of topical steroid	0.96	0.98	0.39 – 2.45	0.96
Immune-mediated sterile melt	1.34	1.68	0.76 – 3.76	0.20
Single CTA application (versus multiple)	2.30	3.09	1.34 – 7.16	0.01

Table 4

Complications and surgical interventions within 1 month of CTA application

Complication ^a	N=61
Neovascularization	17
Stromal inflammation	15
Surgical intervention	
Penetrating keratoplasty	43
Keratoprosthesis	5
Enucleation / Evisceration	3
Amniotic membrane transplant	1
Total	52

^a 61 eyes had recorded glue details