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Efficacy of Cyanoacrylate Tissue Adhesive Application in the Management of Corneal Perforations at Preah Ang Duong Hospital in Cambodia

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Abstract

Purpose: The study was to evaluate the efficacy of cyanoacrylate tissue adhesive (CTA) application in corneal perforations. **Method:** This was a prospective study on 20 patients of corneal perforations who received cyanoacrylate tissue adhesive application as treatment between March 2021 and March 2022 at Preah Ang Duong Hospital. The primary outcome measure was success rate of CTA application, while the secondary outcome was to measure postoperative best-corrected visual acuity (BCVA) and ocular complications. **Results:** The mean age of patients was 44.15 ± 16.05 years old and 7 (35%) were female. Causes of perforation were microbial infection in 12 patients (60%), trauma in 5 patients (25%), and sterile melting in 3 patients (15%). The perforation of size smaller than 1.5 mm was in 8 patients (40%) while 12 patients (60%) had perforated size between 1.5 mm to 3 mm. The perforation was 60% (12 patients) central, 25% (5 patients) paracentral, and 15% (3 patients) peripherally. Out of 20 patients, 5 patients (25%) received CTA application more than 1 time. The mean glue retention was 57.60 ± 31.84 days. Success rate of glue application (defined as intact globe without surgical intervention regardless of number of CTA applications) was 85%. At the last visit, 7 patients (35%) had BCVA of 6/120 or better. Common complications were uveitis (45%), ocular hypertension (30%), cataract (25%) and neovascularization (20%). No serious complications were found. **Conclusion:** Cyanoacrylate tissue adhesive is an effective treatment option in sealing corneal perforations with no serious complications.

Keywords

Cyanoacrylate Tissue Adhesive, Corneal Perforation, Microbial Infection,

Sterile Melting

1. Introduction

Corneal perforation and severe thinning of the stroma (descemetocele) are ocular emergencies which demand intermediate intervention to remain anatomical integrity and visual function. Late treatment leads to visual loss, endophthalmitis, and eventually evisceration. The prevalence is higher in developing countries as compared to developed countries [1] [2]. A study done at Takeo Eye Hospital in Cambodia from 2012 to 2015 stated that 55% of eye removal surgery was caused by corneal perforations [3]. Causes of corneal perforations are categorized into infectious, non-infectious, and traumatic. There are various methods used to seal corneal perforations. These include the use of bandage contact lens, application of tissue adhesives, and surgeries such as amniotic membrane transplantation, corneal patch graft or transplantation [4] [5].

Cyanoacrylate tissue adhesive (CTA) combines cyanoacetate and formaldehyde, and polymerizes upon contact with fluid providing tectonic strength [6]. The use of CTA was first reported in 1968 and became a mainstay treatment for patients with corneal thinning or perforation. Several studies have determined success rates of CTA in corneal perforations ranging from 37% to 63.6% depending on different causes of perforations [7]-[12]. However, the retention of CTA in maintaining the globe integrity and factors associated with glue failure have not been statistically analyzed. Thereafter, the prospective study on approximate 20 corneal perforation patients receiving CTA glue as treatment at Preah Ang Duong Hospital, between 15th March 2021 and 14th March 2022, was conducted to evaluate its outcome.

2. Method

This was a prospective study on patients of corneal perforations who received cyanoacrylate tissue adhesive application as treatment at Preah Ang Duong Hospital, Phnom Penh, Cambodia, from March 2021 to March 2022 after obtaining approval from National Ethics Committee for Health Research (Registration N˚ 040 NECHR dated March 01, 2021). The written informed consent for participation was taken from each patient before the surgery.

Patients of corneal perforation size smaller or equal to 3 mm or with impending corneal perforations were included. Exclusion criteria included perforation involving with sclera, corneal perforation of size larger than 3 mm, presence of endophthalmitis, pan-ophthalmitis, glaucoma, or retinal pathologies, and patients of loss following-up.

Patient's demographic information, past medical and surgical histories, detailed ophthalmic history, ophthalmic medications, ophthalmic comorbidities were questioned and recorded. Patients, then, underwent ocular examination for

assessment of clinical characteristics of corneal perforation including size, location, and etiology.

2.1. Surgical Procedure

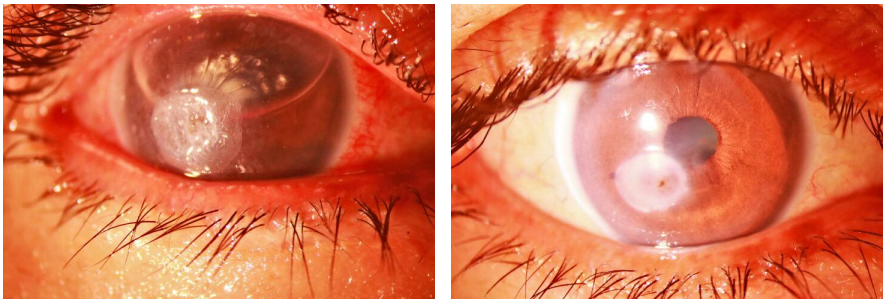
The application of CTA was performed by corneal specialists in the operating theater under topical anesthesia. A wire speculum was used to expose the cornea under operating microscope. Necrotic tissue and corneal epithelium were debrided near the area of perforation with blunt scrapping. The perforation site and surrounding areas were kept dry with sponges. The corneal perforated site was plugged with CTA in a thin film through a 30-gauge disposable needle mounted on a 1ml syringe and the adhesive was allowed to air dry, followed by a bandage contact lens. CTA application was repeated in cases of hypotony, positive Seidel test, and shallow anterior chamber. Postoperatively, patients with infectious causes were prescribed topical treatment according to their etiologies: antibiotics for bacterial infection, antifungals for fungal infection, and acyclovir 3% eye ointment combined with oral acyclovir 400 mg five times a day for viral infection. In addition, patients with trauma and non-infectious causes were prescribed combined tobramycin and dexamethasone (TobraDex) eye drops four times a day. All patients, furthermore, were added cycloplegics and antiglaucoma medication if they were presented with ocular inflammation and high IOP.

2.2. Post-Operative Evaluation

After CTA application, patients were followed up at day 1, 1 week, 2 weeks and every month for 3 months. At each visit, patients were taken their best-corrected visual acuity, progression of signs and symptoms, and the stay of the glue. If the glue was prematurely dislodged with no maintenance of the globe (Seidel test was positive), repeated glue was applied to seal the leaking site. At the meantime, all participants will be assessed for any related ocular complications.

2.3. Data Entry and Analysis

Data entry was done on Microsoft Excel and imported into Statistical Package for Social Sciences (SPSS) software version 23 for Mac for analysis. Specific analytical procedures for data analysis included means, standard deviations and descriptive using frequency and percentage. Next, glue success as a function of time was represented with Kaplan-Meier curve survival analyses. Success of CTA application was defined as an intact globe without surgical intervention regardless of number of CTA applications (**Figure 1**). Each eye was considered one sample (N = 20) and subsequent surgical interventions were counted as events. Visual acuity was converted from Snellen chart to logarithm of the minimum angle of resolution (LogMAR) [13]. Visual acuity of light perception and no light perception were not converted. Wilcoxon signed ranks test was used to compare best-corrected visual acuity (BCVA) before and after glue application. p-value < 0.05 is considered statistically significant.



(a) (b)

Figure 1. (a) Day 1 after Cyanoacrylate Tissue Adhesive application in perforated bacterial keratitis; (b) Same eye showing healed perforation with corneal opacity at last visit (3 months).

3. Results

Twenty-two patients were included in the study, but two patients lost follow-up. Therefore, twenty patients (20 eyes) in the study had the mean age of 44.15 ± 16.05 ranging from 25 to 87 years and 7 (65%) patients were female. Baseline clinical characteristics are shown in **Table 1**. The main causes of corneal perforation were microbial infection (60%), trauma (25%), and non-infectious melt (15%) such as Stevens-Johnson syndrome and Mooren's ulcer. 12 patients or 60% had perforation size between 1.5 mm to 3 mm whereas 8 patients had perforation size of less than 1.5 mm. Corneal perforations were located in 60% central, 25% paracentral and 15% peripheral. 15 patients or 75% required only one CTA gluing while 3 (15%) and 2 (10%) patients required two and three CTA applications respectively. The mean duration of cyanoacrylate glue adhesion to the ocular surface of patients was 57.60 ± 31.84 days with only 20% of patients had their glues dislodged in less than 30 days.

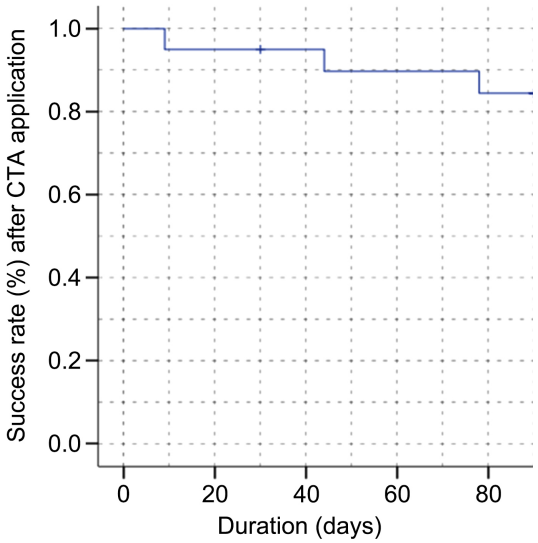
Eighty-five percent (17/20) of eyes treated with CTA had complete resolution of the corneal perforation at the last visit after glue application alone, which was counted as success rate of CTA application outcome. Fifteen percent (3/20) of eyes underwent secondary procedures after glue application and were qualified as failures. Among 3 patients, 1 had amniotic membrane transplantation, 1 had conjunctival hooding and another 1 immunocompromised patient with a severe corneal infection had evisceration (**Table 1**).

The Kaplan-Meier survival curve of CTA application success is shown in **Figure 2**. Success was defined as an intact globe without surgical intervention regardless of the number of CTA applications. The success rate was 95% at 30 days, 90% at 60 days, and 85% at 90 days.

At presentation, 19 patients (95%) had their baseline visual acuity of counting fingers to perception of light and 1 (5%) patient had visual acuity of better than 6/18 (**Table 2**). After CTA application, most patients showed better best corrected visual acuity: 4 patients (20%) were better than 6/18, 2 patients (10%) were between 6/18 to 6/36, 1 patient (5%) was between 6/60 to 6/120, and 11 patients (55%) were between counting fingers to perception of light. 2 patients

Table 1. Demographic and baseline clinical characteristics.

Age, mean (range)	44.15 ± 16.05 (25 - 87)
Sex	
Male	13 (65%)
Female	7 (35%)
Etiology	
Microbial	12 (60%)
Bacterial	7 (35%)
Viral	3 (15%)
Fungal	2 (10%)
Trauma	5 (25%)
Sterile melt (non-infectious)	3 (15%)
Stevens-Jonhson syndrome	2 (10%)
Mooren's ulcer	1 (5%)
Size of perforation (mm)	
<1.5	8 (40%)
≥1.5 - 3.0	12 (60%)
Location of perforation	
Central	12 (60%)
Paracentral	5 (25%)
Peripheral	3 (15%)
Number of glue application	
Once	15 (75%)
Twice	3 (15%)
Trice	2 (10%)
Stay of glue, mean	57.60 ± 31.84
<30 days	4 (20%)
≥30 days	16 (80%)
Outcome of tissue adhesive	
Sealed	17 (85%)
Non sealed	3 (15%)
Surgical intervention	
Amniotic membrane transplant	1 (5%)
Conjunctival hooding	1 (5%)
Evisceration	1 (5%)



Days	0	10	30	60	90
% Success	100	95	95	90	85

Figure 2. Kaplan-Meier curve for cyanoacrylate tissue adhesive application success.

Table 2. Best corrected visual acuity before and after cyanoacrylate tissue adhesive application.

BCVA	At presentation	At 1 month follow up	At the last follow up
>6/18	1 (5%)	1 (5%)	4 (20%)
6/18 - 6/36	0	3 (15%)	2 (10%)
6/60 - 6/120	0	1 (5%)	1 (5%)
CF - PL	19 (95%)	14 (70%)	11 (55%)
NPL	0	1 (5%)	2 (10%)

(10%), however, lost their visual acuity because of severe corneal ulcer and underwent conjunctival hooding and evisceration. Figure 3 shows the mean best-corrected visual acuity at presentation, 1 month and 3 months in patients treated with CTA, and in patients with a successful CTA treatment. For all patients receiving CTA application, the mean baseline BCVA before and after the intervention were 2.22 ± 0.63 and 1.70 ± 0.99 in LogMAR (p = 0.007, Wilcoxon signed ranks test). In patients with a successful CTA treatment, in addition, the mean BCVA before and after gluing were 2.15 ± 0.66 and 1.57 ± 0.99 in LogMAR. There was significant difference between the pre and post glue BCVA with mean of 0.65 ± 0.76 in LogMAR (p = 0.004, Wilcoxon signed ranks test), which means patients with a successful CTA treatment had better BCVA at 3-month follow-up visit.

Complications following CTA application were listed in Table 3. No serious complication such as endophthalmitis nor corneal decompensation was detected.

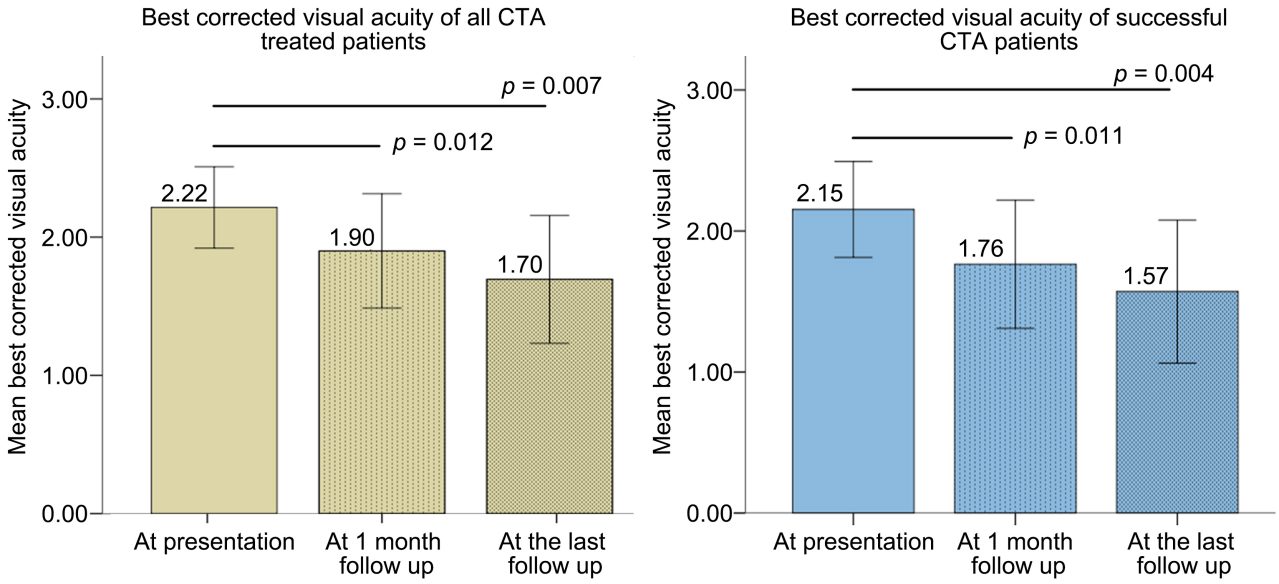


Figure 3. Mean best corrected visual acuity at presentation, 1 month follow-up and the last follow-up.

Table 3. Complications following Cyanoacrylate Tissue Adhesive application.

Complications	Numbers (percentage)
Uveitis	9 (45%)
Ocular Hypertension	6 (30%)
Cataract	5 (25%)
Neovascularization	4 (20%)
None	6 (30%)

The most common side effect was ocular inflammation or uveitis seen in 9 (45%) patients. Ocular hypertension was found in 6 (30%) patients which might be associated with ocular inflammation. Cataract was observed in 5 (25%) patients. 4 patients presented corneal neovascularization at the glue applied area. 6 (30%) patients had no complications.

4. Discussions

In our study, the success rate of CTA application in corneal perforation of smaller than 3 mm was 85% at 90 days. The result was not similar to previous studies which demonstrated the success rate varying from 28% to 91% because of different definitions of success. Yin *et al.* [14] retrospectively studied the outcomes of Cyanoacrylate Tissue Adhesive application in corneal thinning and perforation in 140 eyes and defined the success of CTA application depending on single or multiple applications. Single CTA application success is an intact globe without additional intervention whereas multiple CTA application success is an intact globe without surgical intervention. The success rate at 90 days was 28% and 46% for single and multiple applications respectively. The definition of

multiple CTA application success of Yin *et al.* [14] and of our study were the same but the success rate of Yin *et al.* was lower because of 75% of patients included in their study presented with significant ocular surface diseases, lid abnormality and associated exposure, neurotrophic keratopathy, and dry eye diseases. It increased the risk of corneal melt and perforation. In addition, Tan *et al.* [15] defined similar success CTA treatment as "healing by scarring or until planned corneal procedures" in their study of the efficacy of N-Butyl-2 Cyanoacrylate (Histoacryl) for sealing corneal perforation. The study found 67% of success rate in 30 patients who underwent CTA application. Setlik *et al.* [16], moreover, demonstrated the perforated corneal healing of 40.9% in 22 eyes by single CTA application, 31.8% required penetrating keratoplasty, and 18.18% had adhesive in place at the final visit. They mentioned that penetrating keratoplasty was performed not because of the failed glue but for the belief of offering better visual potential. Thereafter, the success rate of CTA application in Setlik *et al.* study should be higher than 40.9%. Another study of Kasetsuwan *et al.* [17] defined the success of cyanoacrylate gluing as scarring of cornea maintaining the integrity of the eye and reported 91% of success rate in 66 patients. However, they did not mention if 91% of success rate was from CTA application alone or included surgical interventions. The study also added that 25.76% required surgical treatment. Last but not least, Raj *et al.* [18] set criteria of CTA application success as "resolution of infiltrates, vascularization around site of perforation and corneal scarring or opacity". The study revealed 83.58% of successful rate in 67 eyes over period of three months.

Regarding the visual outcomes, our study found there is significant difference between best-corrected visual acuity before and after CTA application with p value of 0.004 and BCVA of 6/120 and better presented in 35% of patients at the final visit comparing to only 5% at baseline. Few studies of outcomes of CTA revealed similar results. Raj *et al.* [18] reported the significant difference between before and after glue application with mean VA of 0.67 ± 0.08 with p value of 0.00 and BCVA of 6/60 and better in 47.76%. Another study of Setlik *et al.* [15] demonstrated the 77.8% of improvement in BCVA among corneal perforation patients healed with tissue adhesive application. Anchouche *et al.* [19] demonstrated that there was significant difference between BCVA at presentation and at 12-month visit of all CTA treated patients (p = 0.04). They also mentioned 43% of patients had BCVA of 6/60 or better at the last visit. Last but not least, kasetsuwan *et al.* [17] reported 80% of patients underwent corneal gluing at the last visit had VA of 6/60 or better. However, they did not mention if VA before and after corneal gluing were statistically significant difference.

In our study, no serious complication was found following CTA application. Most common complications were ocular inflammation or uveitis, ocular hypertension, cataract, and neovascularization. 6 patients or 30% presented with no complication at all. The result was similar to previous studies. Raj *et al.* [18] reported complications following CTA applications such as cataract (19.40%),

uveitis (8.95%), corneal melting (8.95%), and glaucoma (2.98%). He also mentioned 58.20% of patients presented with no complications. In addition, Yin *et al.* [14] stated that complications found after CTA application in corneal thinning and perforation in their study were corneal neovascularization and stromal inflammation. Kasetsuwan *et al.* [17], moreover, detected only corneal irritation developed in 1 out of 66 patients in their study. No serious side effect was reported. Singh *et al.* [20] additionally revealed the complications after CTA application were neovascularization (13%), stromal infiltration (12%) and inflammation (5%). In their study, they explained the terms used of corneal stromal inflammation and infiltration were noted from the retrospective reports which did not differentiate sterilization or infection. No other serious complication was found.

The current study has several limitations. One of the main limitations is small sample size, which cannot represent Cambodian people and might affect the outcome of CTA application. Another limitation is short period of follow-up. Although the critical time of glue failure is at 30 days, few patients still had their glue maintained on the cornea at the last visit and some complications might occur at later time than 3 months. Despite limitations, it is the first study in Cambodia assessing the outcome of cyanoacrylate tissue adhesive application in corneal perforation. The high success rate proves it as an effective treatment option prior to definite surgical interventions such as corneal transplant which is expensive and limited in its accessibility.

5. Conclusion

Cyanoacrylate tissue adhesive application is an effective treatment providing high success rate in sealing corneal perforation of less than 3 mm. It is also considered as a safe procedure with no serious complications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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