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IP International Journal of Ocular Oncology and Oculoplasty

Journal homepage: https://ijooo.org/

Original Research Article

Cyanoacrylate glue: An emerging alternative for sealing of corneal perforation

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ARTICLE INFO

Article history:
Received 03-05-2024
Accepted 21-05-2024
Available online 27-08-2024

Keywords:
Corneal perforation
Tissue adhesive
N butyl cyanoacrylate

ABSTRACT

Background: Maintaining corneal wound integrity is an important goal in corneal perforations resulting from either traumatic or non- traumatic etiology. Tissue adhesives (TA's) are group of synthetic or naturally occurring compounds, which helps in wound reconstruction and have emerged as alternatives to conventional sutures.

Aim: Our study aims to evaluate the efficacy N- butyl cyanoacrylate TA in corneal perforations following infectious keratitis by assessment of its morphological and functional outcome.

Materials and Methods: A prospective observational study conducted over a period of 6 months on 42 eyes of 42 patients with perforated corneal ulcer, fulfilling the inclusion criteria, presenting to our outpatient department. A standard technique was used to apply TA to the site of perforation under topical anaesthesia in all patients and they were followed-up for a period of 6 weeks. Data analysis was done using SPSS software (Version 22) and P value calculated by Pearson Chi-square test (Fisher exact test). P- value < 0.05 was considered statistically significant.

Results: Morphological outcome in this study showed statistically significant relationship with causative organism and size of the perforations ($p<0.05$). The functional outcome showed statistically significant relationship with location of perforation, duration of symptoms and duration of stay of glue ($p<0.05$).

Conclusion: TA's works well when the corneal perforation is <1.5 mm in diameter. The morphological outcome of TA depends upon etiology, size of perforations and complications significantly. Functional outcome of tissue adhesive shows significant association with location of perforation, duration of symptoms and stay of glue.

1. Introduction

Corneal perforation leads to major ocular morbidity with profound visual loss.[1] Infectious perforation occurs more in developing countries than developed countries.[2] H.aegyptius, C.diphtheriae, N.gonorrhoeae, N.meningitidis, Shigella and Listeria can penetrate intact corneal epithelium.[3] Altered epithelial cells and polymorphonuclear cells cause melting of strom[4] leading to perforations.

TAs are group of synthetic or naturally occurring compounds which help in wound reconstruction.[5] Cyanoacrylate glue and fibrin glue have emerged as alternatives to conventional sutures. TA's improve post-operative outcome by reducing inflammation, surgical time without compromising the wound strength. An ideal TA should be bio-compatible, optically clear, accessible, affordable, non- inflammatory, non-infectious and disappear eventually to permit healing at the interface. Cyanoacrylate and fibrin both are effective for corneal perforations of size of within 3 mm.[6]

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https://doi.org/10.18231/j.ijooo.2024.017

Our study aims to evaluate the efficacy of N-butyl cyanoacrylate in corneal perforations following infectious keratitis by assessment of its morphological and functional outcome.

2. Materials and Methods

This is a prospective observational study conducted over a period of 6 months on 42 eyes of 42 patients with perforated corneal ulcer, between the age 40-70 years, presenting to outpatient department of our institute. The institutional research and ethical committee approval was obtained before commencing this study. The research was in accordance to the tenets set forth in the Declaration of Helsinki.

2.1. Inclusion criteria

All corneal perforations of size ≤3.0mm within 6mm radius from central apex of cornea[7] between the age 40- 70 years and willing to give written informed consent and for at least 6 weeks of follow-up were included in the study. All patients were operated by single surgeon to rule out surgical bias.

2.2. Exclusion criteria

Perforations with scleral or limbal involvement, associated endophthalmitis or panophthalmitis were excluded from the study.

2.3. Application of tissue adhesive

2.3.1. Procedure

A standard technique was used to apply TA at the site of perforation.[8] Topical anaesthesia was used. A wire speculum was applied to expose the cornea under operating microscope. Necrotic tissue and surrounding loose epithelium at site of perforation was scraped with a blunt crescent and peeled with fine forceps. The corneal scraping was sent for microbiological examination to identify the causative organism. The perforation site was dried with sponges. The corneal perforation site was plugged with TA in a thin film through a 30-gauge disposable needle mounted on a 1ml syringe or insulin syringe. The adhesive was allowed to air dry. Bandage contact lens was applied after drying up of the TA in all the cases.

Postoperatively, all patients were commenced on empirical treatment depending upon the etiology in the form of topical antibiotics, antifungals, antivirals, cycloplegics, antiglaucoma drugs, tear substitutes and acetazolamide tablets.

All the patients were followed up for a period of 6 weeks. Visual acuity, slit-lamp examination to monitor the sealing of ulcer and the status of glue were done on Day 1, 1^{st} week, 3^{rd} week and 6^{th} week (Figure 1). Clear cornea, residual corneal opacity and requiring TPK were the three categories in which the morphological outcome of the subjects was analyzed, while for functional outcome BCVA at end of 6 weeks was taken into account.

2.4. Data analysis

Data analysis was done using SPSS software (Statistical Package for Social Sciences, version 22, SPSS Inc, Chicago, IL). Statistical data were expressed in terms of means ± standard deviations (mean ± SD). The frequency and percentage were expressed for descriptive statistics. Comparison of BCVA before and after glue application was carried out by using Pearson chi-square test (Fischer exact test). P- value < 0.05 was considered statistically significant.

3. Results

42 eyes of 42 patients were included in our study. The mean age of the study population was 58.14 ± 6.31 years. Our study showed a male predominance 27 (64.29%). Right eye was involved in majority of patients 23 (54.76%) (Table 1).

Table 1: Demographic characteristic of study population

		No. of subjects (n=42)	Percentage (%)
Age	40 - 50yr	6	14.29
	50 - 60yr	11	26.19
	60 -70yr	25	59.52
Gender	Male	27	64.29
	Female	15	35.71
Affected eye	Right	23	54.76
	Left	19	45.24
Etiology	Fungal	16	38.10
	Bacterial	22	52.38
	Viral	4	9.52

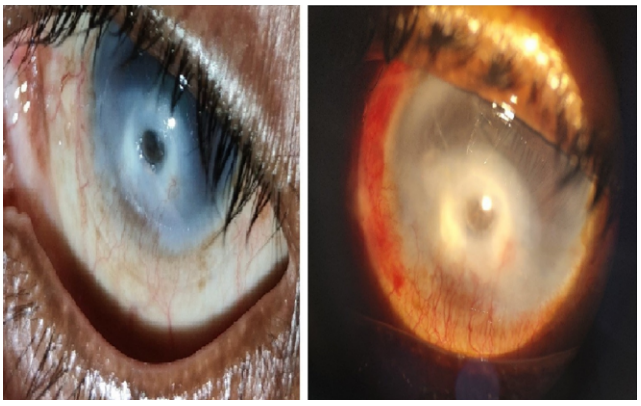

Figure 1: Pre-operative and post-operative image of corneal perforation after application of cyanoacrylate glue

3.1. Characteristics of corneal perforations

Bacterial keratitis constituted bulk of etiology for corneal perforations 22 (52.38%). Other causes included 16 (38.10 %) fungal, and 4 (9.52%) viral infection. 31(73.81%) corneal perforations were of size of 1.6-3.0mm. 23(54.76%) of corneal perforations were paracentral (≥ 3 mm-6mm from centre of cornea) in location. 29(69.05%) cases had one week old symptoms. In 30(71.43%) cases glue stayed or sloughed out in <30 days with mean duration of stay of glue 24.26 ±7.12 days. In only 5 cases the glue was removed to look for the perforation, but all of them were healed completely. No case of any secondary corneal infection was observed (Table 2).

A total of 27(64.29%) cases healed by grade III [leucomatous] corneal scarring and among all these cases corneal vascularization was observed. 7(16.67%) cases healed by grade I [Nebular] / grade II [Macular] corneal scarring and out of these 5 (45.46%) cases had size of perforation <1.5mm. 8(19.04%) cases underwent TPK. None of the patients landed in phthisis bulbi. Morphological outcome showed statistically significant relationship with causative organism, and size of the perforations with p values 0.007 & 0.0035 respectively which is described in Table 3.

At presentation 31(73.81%) patients had BCVA 6/60 to 1/60 and at 6 weeks follow up 28 (66.67 %) patients could get the BCVA > 6/60. 2 (4.76%) patients were denied perception of light (PL) at 6 weeks follow up out of which 1 (2.38%) patient was PL denied at time of presentation. The functional outcome showed significant relationship with location of ulcer, duration of symptom at time of presentation, and duration of stay of glue with p value 0.007, 0.004 and 0.00003 respectively which is described in Table 4.

Corneal melting was observed in 5(11.91%) of cases and out of these cases 2 (40%) had perforation > 1.5 mm who eventually underwent TPK. Out of these, 3 were bacterial in origin and 2 were fungal. 6 non-sealed corneal perforations eventually required TPK. None of the cases got endophthalmitis or pthisical globe.

4. Discussion

Tissue adhesives are considered as standard management for small corneal perforations up to 3-mm.[9] Their antibacterial properties help in arresting the progression of keratolysis.[10] It stays at wound site for a longer duration due to its non-biodegradability.

Tissue adhesive acts as a temporary measure to provide support to the tissue and helps in delaying PK which eventually can be the definitive therapy. Large perforated corneal ulcers constitute the major indication for TPK.[11]

Cyanoacrylates are ester derivatives of cyanoacrylic acid. This method is best suited to perforations that measure less than 3 mm in diameter, are concave in profile, and located away from the limbus. The latter due to the poor adhesion that occurs between the glue and the conjunctival tissue, and the tendency for the adhesive to dislodge when applied in this location.[12–14]

Cyanoacrylates are also bacteriostatic, particularly against gram-positive organisms including Staphylococcus aureus, Streptococcus pneumoniae, and group A Streptococci, due to the absence of a lipopolysaccharide capsule among these pathogens.[15] Application of cyanoacrylate adhesive to an ulcer bed disrupts stromal melting, in both infective and noninfective cases. Cyanoacrylates inhibit re-epithelialization and consequently inhibit the polymorphonuclear leucocytic infiltration in the diseased area.[16,17]

In our study the major etiology of perforated corneal ulcers was bacterial (52.38%).

Our study showed a male predominance of 64.29% which was comparable with that of the study by Prakash et al (84.6%). Hirst et al[18] have reported lower enucleation rate and better visual results after application of TA in corneal perforations. Leahey et al[19] reported the efficacy of N-butyl cyanoacrylate TA for perforations of the conjunctiva, cornea, and sclera. Therefore, TA have been used to treat corneal perforations of all kind of etiologies.

The N-butyl cyanoacrylate was used as the TA in the present study in perforation ≤3.0mm in size. 73.81% of perforations in the present study were 1.6- 3.0mm in size. The clinical picture after the time of application of TA was assessed by the size of the infiltrate, corneal vascularization and corneal scarring. Lekskul M et al[20] reported that TA works well when the corneal perforation was<1.0 mm in diameter, away from limbus, and is concave in shape with a crater for the TA to adhere on it. They reported 93.3% of sealing of corneal perforation which was in accordance with our study in which 85.71% were sealed. Garg et al.[21] reported leucomatous corneal scarring in 63.3% cases after application of TA which is almost similar to our study where healing occurred by grade III corneal opacification in 64.29% of cases.

In present study various outcomes of corneal gluing with tissue adhesives were analyzed in reference to morphological and functional outcome. It was found that 85.71% perforations were sealed with glue application and in 14.29% cases TA failed to seal the perforation and these cases eventually required TPK.

The duration of symptoms and location of perforation did not show significant relation with morphological outcome which is in concordance to observations by Garg et al.,[21] but showed statistically significant functional outcome (p value 0.004, 0.007 resp). TA remained or stayed for a mean 26.45 ±6.24 days. In the present study in 28.57% cases the glue stayed for > 30 days and all these cases healed which shows consistency with the observation reported by Garg et al.[21]

Table 2: Morphological and functional characteristic

		No. of subjects (n = 42)	Percentage (%)
Size of perforation	≤1.5 mm	11	26.19
	1.6 – 3.0 mm	31	73.81
Location of perforation	Central	19	45.24
	Paracentral	23	54.76
Duration of symptoms	< 1 week	29	69.05
	1 -2 week	13	30.95
Stay of glue	< 30 days	30	71.43
	≥ 30 days	12	28.57
Outcome of tissue adhesives	Sealed	36	85.71
	Non – sealed	6	14.29
Morphological outcome	Grade III corneal opacity	27	64.29
	Grade I/II corneal opacity	7	16.67
	Needed TPK	8	19.04
	Pthisis bulbi	0	0.00
Functional outcome [BCVA]	>6/60	28	66.67
	6/60 – 1/60	8	19.04
	<1/60	6	14.29

* BCVA: Best corrected visual acuity **TPK- Total Penetrating Keratoplasty ***PL – Perception of light

Table 3: Association of morphological outcome in corneal perforation with various parameters

Variables	**Morphological outcome**			
	Grade III corneal opacity N (%)	**Grade I / II corneal opacity N (%)**	**Needed TPK N (%)**	**p-value**
Age(years)				
40-50	4 (66.66%)	1 (16.67%)	1 (16.67%)	
50-60	6 (54.55%)	3 (27.27%)	2 (18.18%)	p = 0.878
60-70	17 (68.00%)	3 (12.00%)	5 (20.00%)	
Etiology				
Fungal	7 (43.75%)	3 (18.75%)	6 (37.50%)	
Bacterial	19 (86.36%)	2 (9.09%)	1 (4.55%)	**p = 0.007**
Viral	1 (25.00%)	2 (50.00%)	1 (25.00%)	(<0.05)
Size of perforation				
≤1.5 mm	3 (27.27%)	5 (45.46%)	3 (27.27%)	**p = 0.0035**
1.6 – 3.0 mm	24 (77.42%)	2 (6.45%)	5 (16.13%)	(<0.05)
Location of perforation				
Central	9 (47.37%)	4 (21.05%)	6 (31.58%)	p = 0.088
Paracentral	18 (78.26%)	3 (13.04%)	2 (8.70%)	
Duration of symptoms				
<1 week	20 (68.97%)	6 (20.69%)	3 (10.34%)	p = 0.127
1-2 week	7 (53.85%)	1 (7.69%)	5 (38.46%)	
Stay of glue (days)				
<30	19 (63.33%)	5 (16.67%)	6 (20.00%)	p = 1.0
≥30	8 (66.66%)	2 (16.67%)	2 (16.67%)	
Complications				
Corneal melt	3 (60.00%)	0 (0.00%)	2 (40.00%)	
Others	6 (46.15%)	2 (15.39%)	5 (38.46%)	**p = 0.042**
None	18 (75.00%)	5 (20.83%)	1 (4.17%)	(<0.05)

Table 4: Association of functional outcome in corneal perforation with various parameters

Variables	Functional outcomes			
	>6/60	6/60 – 1/60	<1/60	p-value
Age (years)				
40-50	3 (50.00%)	2 (33.33%)	1 (16.67%)	
50-60	7 (63.64%)	1 (9.09%)	3 (27.27%)	p = 0.415
60-70	18 (72.00%)	5 (20.00%)	2 (8.00%)	
Etiology				
Fungal	14 (87.50%)	1 (6.25%)	1 (6.25%)	
Bacterial	12 (54.55%)	6 (27.27%)	4 (18.18%)	p = 0.18
Viral	2 (50.00%)	1 (25.00%)	1 (25.00%)	
Size of perforation				
≤1.5 mm	8 (72.73%)	2 (18.18%)	1 (9.09%)	p = 1.0
1.6 – 3.0 mm	20 (64.52%)	6 (19.35%)	5 (16.13%)	
Location of perforation				
Central	8 (42.10%)	6 (31.58%)	5 (26.32%)	**p = 0.007**
Paracentral	20 (86.96%)	2 (8.70%)	1 (4.34%)	(<0.05)
Duration of symptoms				
<1 week	23 (79.31%)	5 (17.24%)	1 (3.45%)	**p =0.004**
1-2 week	5 (38.46%)	3 (23.08%)	5 (38.46%)	(<0.05)
Stay of glue (days)				
<30	26 (86.66%)	2 (6.67%)	2 (6.67%)	**p = 0.00003**
≥30	2 (16.67%)	6 (50.00%)	4 (33.33%)	(<0.05)
Morphological outcomes				
Grade III Corneal opacity	20 (74.07%)	3 (11.11%)	4 (14.82%)	
Grade I/II Corneal opacity	3 (42.86%)	3 (42.86%)	1 (44.28%)	p = 0.34
Needed TPK	5 (62.50%)	2 (25.00%)	1 (12.5%)	
Complications				
Corneal melt	2 (40.00%)	1 (20.00%)	2 (40.00%)	
Others	7 (53.84%)	3 (23.08%)	3 (23.08%)	p = 0.113
None	19 (79.16%)	4 (16.67%)	1 (4.17%)	

P Value calculated by Pearson Chi-square test (Fisher exact test)

who reported that the infiltrate ultimately resolved in cases where the adhesive had been left on the cornea for more than one month.

In our study, morphological outcome showed statistically significant relationship with causative organism (p=0.007) and size of the perforations (p=0.0035). The functional outcome showed significant relationship with duration of stay of glue (p=0.00003).

5. Conclusion

The major objective in treating a patient with a corneal perforation is to restore the integrity of the globe and useful vision. This goal may require an array of procedures. The goals of initial intervention are to seal the perforation and restore the integrity of the globe. This should be done as rapidly as possible to minimize risk of peripheral anterior synechiae, cataract formation and intraocular infection.

Tissue adhesive works well when the corneal perforation is <1.5 mm in diameter at the level of Descemet's membrane, is concave in shape with a crater for the tissue adhesive. In many cases, tissue adhesive is sufficient treatment that promotes healing and scarring and obviates the need for further surgery. Tissue adhesive is left in situ for several months until it dislodges spontaneously. Adhesive has been shown to be bacteriostatic to gram-positive (but not to gram-negative) organisms and to slow stromal-melting. Adhesive gives tectonic support to the stroma through vascularization and fibroplasia.

The morphological outcome of TA depends upon etiology, size of perforations and complications significantly. Functional outcome of tissue adhesive shows significant association with location of perforation, duration of symptoms and stay of glue.

The cases in various subgroups were relatively fewer to arrive at definitive conclusions.

A small sample size, short follow-up period, poor socio-economic status of study population and high cost of treatment were the major limitations that were faced in our study.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Wahi D, Khanna V, Kumar R. Cyanoacrylate glue: An emerging alternative for sealing of corneal perforation. *IP Int J Ocul Oncol Oculoplasty* 2024;10(2):85-90.