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The Efficacy of N-Butyl-2 Cyanoacrylate (Histoacryl) for Sealing Corneal Perforation: A Clinical Case Series and Review of the Literature

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Abstract

Purpose: To investigate the efficacy of corneal gluing procedures for corneal perforations of mixed aetiologies in a tertiary eye hospital in Sydney, Australia.

Design: Retrospective case series.

Methods: Episodes of corneal gluing procedures were identified from the Sydney Eye Hospital surgical database over 42 months from January 2010. All gluing procedures in this study were conducted in the operating theatre. Categorical variables were compared using Pearson's chi-square test.

Results: Forty-five episodes of corneal gluing using n-butyl-2-cyanoacrylate were identified from 30 eyes. 18 eyes were glued once, 9 eyes were glued twice and 3 eyes were glued thrice. The median duration of butyl-cyanoacrylate adhesion was 14 days, range 1 to 1945 days. Our data yielded an episodic success rate of 67% for n-butyl-2-cyanoacrylate gluing when success was defined as the tissue adhesive sealing the leak until healing by scarring or until planned definitive surgery. Secondary outcomes included success rate by the location, aetiology, and size of the corneal perforation, and did not reach statistical significance. Of our 30 eyes treated with n-butyl-2cyanoacrylate glue, 47% (n=14) did not require further surgical intervention and healed by scarring. The complications noted with n-butyl-2-cyanoacrylate use were cornea vascularisation (n=5), conjunctival and corneal irritation (n=2), and secondary microbial keratitis (n=1).

Conclusions: Corneal gluing using n-butyl-2-cyanoacrylate was successful in 67% of episodes. Almost half of our eyes healed without surgical intervention. Corneal gluing, previously thought to be a temporising measure, is effective and can potentially be a definitive treatment.

Keywords: Cyanoacrylate; Corneal glue; Histoacryl; Corneal perforation; Mixed aetiologies; Glue efficacy

Introduction

Corneal perforation is an ophthalmic emergency requiring immediate intervention as it can lead to grave visual outcomes [1]. Current treatment options for cornea perforations include lamellar and full-thickness patch grafts, penetrating keratoplasty, conjunctival flaps, tissues adhesives, and bandage contact lenses [2,3]. Cyanoacrylates are increasingly used as tissue adhesives for corneal perforations. Sealing cornea perforations with cyanoacrylate glue is often regarded as a temporising measure buying time to treat infection, control inflammation and manage systemic diseases while awaiting favourable treatment environment [4].

Cyanoacrylates are esters of cyanoacrylic acid with alkyl side chains which polymerise in contact with water or weak base through a chemical process called hydroxylation [5]. Advantages of cyanoacrylate are relative ease of application, ready availability, long shelve-life, low cost, low toxicity, and similar if not better clinical outcomes compared to other corneal sealants such as fibrin glue and polyethylene glycol [5]. Studies from pig eyes demonstrated a mean leakage pressure of 107 ± 31.15 mmHg with cyanoacrylate, which was similar to conventional nylon sutures for perforated cornea [6]. Besides physical sealing of corneal defects, cyanoacrylate was also reported to inhibit keratolysis by arresting the migration of polymorphonuclear leukocytes to the site of a cornea "melt" [7,8]. In addition, it exhibits anti-microbial activities, especially to common Gram-positive pathogens such as Staphylococcus species and Streptococcus species [9]. An in vitro study of cyanoacrylate showed growth inhibition of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Escherichia coli* and *Enterococcus faecalis*, but it was reported to have no bactericidal activity against Pseudomonas species [9].

In comparison to conventional suturing, cyanoacrylate glue application is cheaper, quicker, easy to apply, induces less curvature changes and has anti-bacterial properties but is limited to perforation size less than 3 mm [5,6].

The use of cyanoacrylate tissue adhesive to seal corneal perforations is a relatively new approach and reported studies in literature focused on specific corneal diseases (Table 1). We believe that cyanoacrylate

has potential for suture-less corneal surgeries. However, there are limited efficacy data on cyanoacrylate use on mixed aetiologies. To assess the efficacy and safety of cyanoacrylate use, a review of cyanoacrylate glue use on corneal diseases of mixed aetiologies is necessary before assessing efficacy on surgical wounds.

Citations	n=	Study Type	Location	Reported Outcome
[10]	Perforated cornea (n=22) (Isobutyl-cyanoacrylate)	Retrospective case series	USA	40.9% healed with adhesive alone. 31.8% needed PK. 27.3% multiple application.
[11]	Perforated fungal keratitis (n=66) (Butyl-cyanoacrylate)	Retrospective case series	India	63.6% infiltrate resolved with scar formation. 37.8% multiple application. 24.2% worsening keratitis. 12.1% successful PK.
[12]	Perforated herpetic keratitis (n=46) (Butyl- cyanoacrylate)	Retrospective case series	Australia	57% needed PK. 37% complete healing. 31% multiple application. 4% evisceration.
[15]	Impending and perforated corneas (n=66) (Ethyl- cyanoacrylate)	Retrospective case series	Thailand	91% successful. 26% required definitive treatment.
[17] (this study)	Mixed Aetiologies of perforated cornea N=45 (Butyl-cyanoacrylate)	Retrospective case series	Australia	67% successful as definitive and temporising measure. 47% healed with adhesive alone.
[18]	Fibrin (n=19) Cyanoacrylate (n = 22) (Butyl- cyanoacrylate)	Randomised controlled clinical trial	India	Both effective. Fibrin glue healed faster. Fibrin glue induced less cornea vascularisation. Fibrin glue required longer time for adhesive plug formation.
[19]	Corneal (n=2) Bleb leak (n=2) (Octyl-cyanoacrylate)	Case series	Japan	All effective. Several applications required. No adverse clinical effects.

Table 1: Summary of clinical trials involving cyanoacrylate in past 10 years.

Methods

We carried out a retrospective clinical records review of corneal perforation cases treated with n-butyl-2 cyanoacrylate glue at the Sydney Eye Hospital, Sydney, a tertiary referral centre for severe corneal diseases. The study period was January 2010 to July 2013. Ethical approval was obtained from the Human Research Ethics Committee of the Prince of Wales Hospital, Sydney, Australia (HREC number 12/273 (LNR/12/POWH/540)) and complied with the tenets of the Declaration of Helsinki.

N-butyl-2 cyanoacrylate glue (Histoacryl® by B. Braun Tuttlingen/ Germany) was used in all instances. The rationale for butyl side group is because cyanoacrylates with shorter alkyl side chain was thought to be more toxic while those with longer alkyl side chain polymerises slower [5]. All glue applications in this study were performed under sterile conditions in the operating theatre under topical or peribulbar anaesthesia. Seven experienced corneal specialists made clinical decisions on and carried out the application of cyanoacrylate glue to corneal perforations. In instances of anterior chamber shallowing, balanced salt solution was used to reform the anterior chamber. Necrotic tissue on the ocular surface was debrided prior to glue application.

Histoacryl glue was drawn up into a sterile 1.0mL syringe, the corneal surface was dried using sterile cotton spears and a small amount of glue was carefully dropped over the perforation site with a 27-gauge needle. The glue was left to set over at least 30 seconds. Seidel sign negativity was observed with reformed anterior chamber at the end of procedure. A bandage contact lens was applied for comfort and to reduce the risk of pre-mature dislodgement of the tissue adhesive.

Demographic, outcome, and safety data were collected. We defined "success" episodes as the glue sealing the perforation until complete healing by scarring or until planned corneal surgery. Some eyes required several episodes of gluing. Secondary outcome measures including duration of glue adherence, location of perforation, perforation size and aetiologies causing perforation were also recorded. Statistical analysis was performed with SPSS software version 21 (IBM/SPSS Inc, Chicago, IL). Categorical variables were compared using Pearson's chi-square test. P-values less than 0.05 were deemed statistically significant.

Results

A total of 30 eyes over the period of 42 months, commencing January 2010 were identified. On these eyes, there were a total of 45 episodes of n-butyl-2 cyanoacrylate glue application. The median age of our patients was 69 years with an average age of 65 (range 17 to 90 years). 28 of the episodes were performed on left eyes (62%) and 17 were on right eyes (38%). The male to female ratio was 2.5:1. The median duration of glue adherence on living human cornea in our study was 14 days with an average of 99 days (range 1 to 1945 days).

With "success" defined as n-butyl-2 cyanoacrylate sealing corneal perforation by scarring or sealing the leak until planned surgical

procedure per episode, we yielded a success of 67% (n=30) out of 45 episodes of gluing. Eyes maybe glued up to 3 episodes until healing by scarring or planned surgical procedures, these are considered success episodes. Eyes that leaked prematurely within 48hours of glue application were offered emergency surgeries. These are penetrating keratoplasty (n=10), lamellar patch graft (n=5), and evisceration (n=1). The types of failure noted in our study by episodes were persistent leak (n=7) and pre-mature dislodgement (n=9).

Out of 30 eyes treated, the rate of healing of corneal perforation per eye using n-butyl-2 cyanoacrylate and a bandage contact lens without further surgical intervention was 47% (n=14). 18 eyes were glued once, 9 eyes were glued twice and 3 eyes were glued thrice over the duration of our study.

The aetiology of corneal perforation episodes treated with gluing was infective 56% (n=25), dysplastic 20% (n=9), traumatic 13% (n=6) and autoimmune 11% (n=5) eyes. For eyes requiring episodes of re-applications of the glue, the initially established aetiology was assumed to be still active. For traumatic perforations, re-applications were performed for pre-mature dislodgements after secondary infectious aetiologies were excluded.

Within the infective subgroup, there were 16 episodes of bacterial keratitis, 11 viral keratitis episodes (10 herpes simplex virus and 1 varicella zoster virus). There was no fungal keratitis. There was one episode of herpetic keratitis complicated by pseudomonal keratitis.

The location of the perforation were central in 22% (n=10), para-central in 38% (n=17), and peripheral in 40% (n=18) of the 45 episodes of gluing. Perforation size was defined by their largest dimension. Small perforation was less than 1 mm. Medium was 1 mm or larger but less than 2 mm. Large was 2 mm or larger but less than 3 mm. Gluing was performed on small perforations in 35% of episodes (n=16), 45% (n=20) for medium and 20% for large (n=9).

There was no significant difference in the success rate of gluing episode for the different aetiologies (Pearson's chi-square test, p=0.636, Figure 1). Similarly, there was no difference in gluing episode success based on perforation size (p=0.976, Figure 2), or location (p=0.801, Figure 3). Therefore, success rate did not depend on perforation size in our study and the location of perforation had no bearing on success rate.

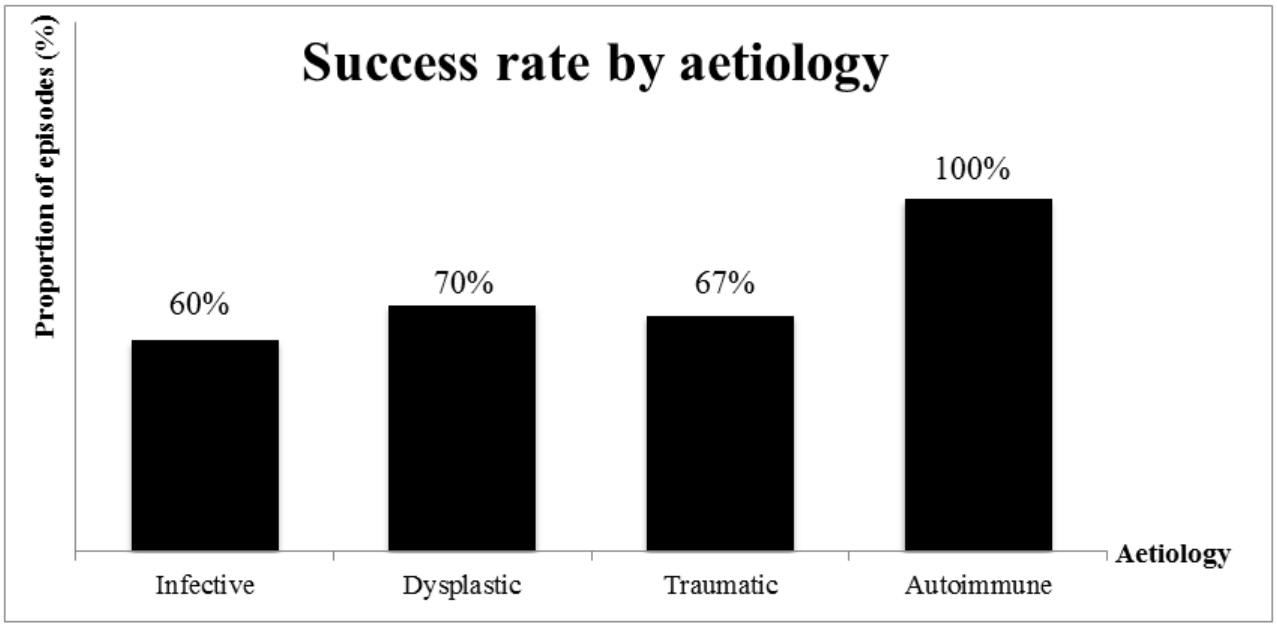

Figure 1: Success rate of corneal perforation episodes by identified aetiology. Chi-square p-value: 0.636 (not significant).

Documented complications with using n-butyl-2 cyanoacrylate in our study were cornea vascularisation (n=5), patient reported ocular discomfort (n=2), and secondary microbial keratitis (n=1). The case of secondary microbial keratitis was a perforated herpes simplex keratitis complicated by pseudomonal keratitis; this eye was eviscerated.

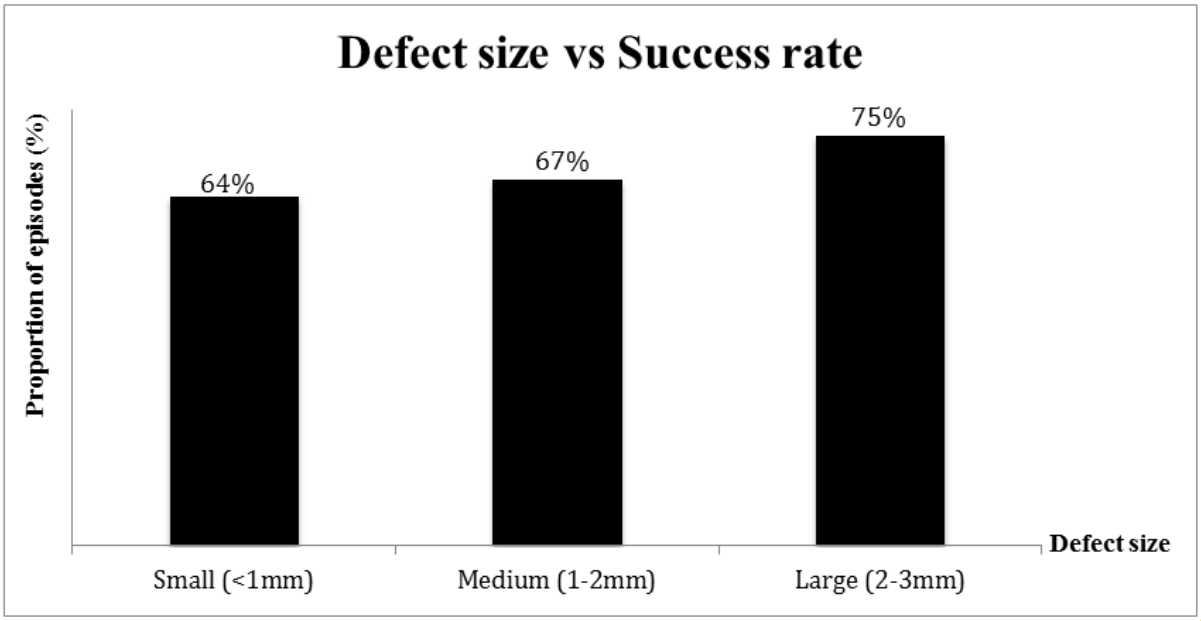

Figure 2: Success rate of corneal perforation episodes by defect size. Chi-square p-value: 0.976 (not significant).

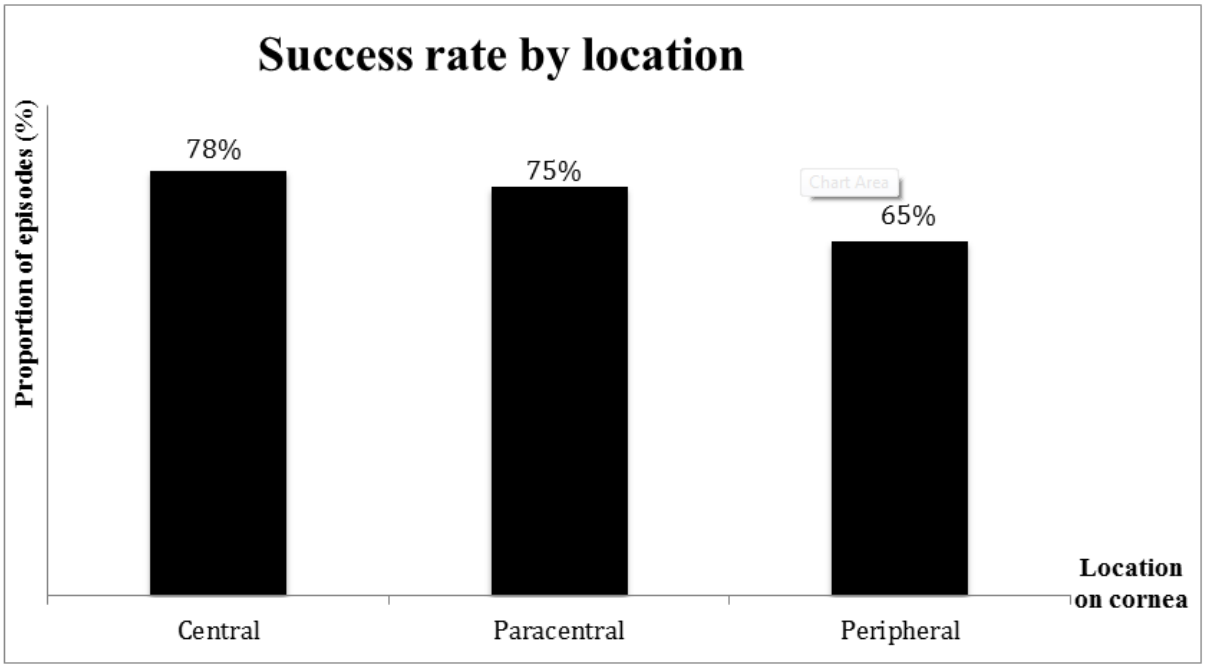

Figure 3: Success rate for corneal perforations episodes by location on the cornea. Chi-square p-value: 0.801 (not significant).

Discussion

Our data revealed an episodic success rate of 67% when n-butyl-2 cyanoacrylate was used to seal corneal perforations less than 3mm of mixed aetiologies. We defined "success" as episodes of gluing until healing by scarring or until planned corneal procedures. There are variations of "success" definitions in the literature for cyanoacrylate corneal glue. We have chosen our definition as such to give clinicians an expected success rate with each episode of glue application as often more than once application of the glue is required.

Setlik et al. [10] reported healing of 41% of their 22 eyes by a single application of isobutyl cyanoacrylate glue, 32% required penetrating keratoplasty while glue was adherent and 27% required more repeated

glue application. It was unclear if the 32% requiring penetrating keratoplasty was due to persistent leak or for better visual outcomes. In our study, 47% of our eyes did not require further intervention apart from n-butyl-2 cyanoacrylate glue and contact lens re-application, and this is similar to the 41% reported by Setlik et al. [10] which healed by isobutyl cyanoacrylate glue alone.

Garg et al. [11] reported healing by scarring in 64% of 66 eyes treated for perforated fungal keratitis with n-butyl cyanoacrylate combined with topical natamycin 5% and oral ketoconazole. In 12% of their eyes, n-butyl cyanoacrylate maintained structural integrity until penetrating keratoplasty and 38% of their eyes required multiple glue applications [11]. We did not document any fungal cases and hence our results are not directly comparable. Nevertheless, butyl-cyanoacrylate were used in both studies and yielded similarly favourable results.

Moorthy et al. [12] reported a lesser success rate of 37% in 46 eyes treated for perforated herpetic stromal keratitis with n-butyl cyanoacrylate glue in addition to antiviral therapy. They reported that therapeutic keratoplasty had to be performed on 57% of their eyes because of failure of the glue [12]. Thirty percent of their eyes required multiple glue applications [12]. It was unclear if multiple glue applications resulted in eventual healing or if the glue deemed to have failed after one application and keratoplasty was performed. Weiss et al. [13] also noted poorer success rate and higher complication rates with herpetic perforations treated with cyanoacrylate. The lower success rate was thought to be due to the secretion of glycoprotein by herpes virus, severe immune response and rapid stromal melt [14]. In our study, there was no statistically significant differences when perforated herpetic keratitis was compared to other aetiologies.

Kasetsuwan et al. [15] reported high success rate of 91% in 66 eyes treated for mixed aetiologies of cornea perforation using shorter alkyl side chain ethyl cyanoacrylate. This success rate included patients who were glued up to five times before glue was deemed a failure [15]. In this study, 26% of patients still required definitive surgical treatment. 15 It was not clear if these eyes had ethyl-cyanoacrylate adherent to the ocular surface at the definitive corneal procedure.

Literatures on cyanoacrylate corneal glue have different definitions of "success". Furthermore, the decision to repeat gluing and offer other surgical interventions is highly dependent on individual clinician's preferences. Hence the reported success rates of cyanoacrylate glue are variable. From available studies, the success rate of cyanoacrylate treating corneal perforation as the sole agent despite multiple applications per eye is approximately 40-60%. This suggests that although cyanoacrylate is often viewed as a temporizing measure, it is in fact the definitive therapy in almost half of patients treated.

The carbon length of the alkyl side chain of cyanoacrylate is inversely proportional to rate of degradation and release of toxic by-products cyanoacetate and formaldehyde [9]. These degradation by-products can cause inflammatory reaction that manifest as scarring, vascularisation, symblepharon and giant papillary conjunctivitis [16]. Shorter alkyl side chains are hence thought to be more toxic [4].

In a study investigating ethyl cyanoacrylate the authors reported only one case of corneal inflammation out of 66 eyes [15]. This was less than expected. In our study, we used n-butyl-2 cyanoacrylate corneal glue and noted 5 eyes with cornea vascularisation and 2 eyes with ocular irritation out of 30 eyes. The toxic response to degradation by-products from cyanoacrylate is cumulative and duration dependent, the low rate of complications reported by the ethyl cyanoacrylate study could be due to shorter duration of cyanoacrylate exposure [15]. The reporting of complications from cyanoacrylate use is variable. In some studies, further leakage around the glue was considered a complication rather than failure [10]. In our study, leakage from gluing within 48 hours was considered treatment failure and emergency surgery was performed.

Cyanoacrylate corneal glue application is associated with frequent pre-mature glue dislodgement. For this reason and for patient comfort, a bandage contact lens was used in all our cases. Data reported by Kasetsuwan et al. [15] revealed 30% of their patients requiring 2 to 5 episodes of gluing before healing or a definitive procedure, while Moorthy et al. [12] suggested that 31% of their eyes had multiple applications of gluing for perforated herpetic keratitis. Garg et al. [11] reported 34% of their eyes requiring 2 to 5 episodes of gluing for perforated fungal keratitis. Our data revealed 40% of eyes required multiple glue applications. Our higher multiple application rates might reflect severe and advanced underlying disease pathology as we are a tertiary eye referral centre in Australia.

The median duration of cyanoacrylate adherent on living human cornea in our study was 14 days (1 day to 1945 days). In other studies, the average duration was 39 days for perforated herpetic keratitis (1 day to 395 days), 12 and 52 days for perforated fungal keratitis (1 day to 255 days) [11]. We had two unusual cases in which n-butyl-2 cyanoacrylate corneal glue remained adherent for extended periods of 782 days and 1945 days [17]. We hypothesize that n-butyl-2 cyanoacrylate glue was able to attach itself to the corneal stroma which has a low cell turnover rate. Pre-mature dislodgement is likely due to adhesion to superficial epithelial layers with a high turnover rate [17]. If prolonged adhesion is desired, removal of superficial epithelial layers prior to glue application could be considered.

Conclusion

In conclusion, the efficacy of corneal gluing procedure using n-butyl-2 cyanoacrylate was 67%. Our success was defined as the episodic sealing of corneal perforation until healing or until planned surgical procedure. Single or multiple applications of n-butyl-2 cyanoacrylate with bandage contact lens healed 47% of our 30 eyes and these eyes did not require further surgical intervention. Based on our findings, although previously thought to be a temporising measure, n-butyl-2 cyanoacrylate can be used as definitive treatment for corneal perforations less than 3mm. Close monitoring is required for frequent pre-mature glue dislodgement and other glue-related complications.

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3. Idea conception and design was by Jackie Tan & Stephanie Watson. Data collection and literature review was by Jackie Tan. Statistical expertise was offered by Yi-Chiao Li. Data analysis and interpretation was by Jackie Tan & Yi-Chiao Li. Manuscript was prepared by Jackie Tan, critical revision of the article was by Yi-Chiao Li, Stephanie Watson & John Foster. All authors were involved in the final approval of the article.

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