Original Article

Morphological and functional outcome of N- butyl cyanoacrylate tissue adhesive application in corneal perforations

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Abstract

Introduction: This study was conducted to characterize morphological and functional outcome of application of tissue adhesive (TA) in corneal perforations.

Methods: This is a retrospective study in which data of corneal perforations which were managed by application of TA (N- butyl cyanoacrylate) from January 2015 to April 2018 were reviewed. The final outcome of TA in corneal perforation was considered as sealed or non-sealed over a period of three months. Criteria of success of TA application included resolution of infiltrates, corneal vascularisation and scarring. Morphological outcome was considered as corneal scarring, required therapeutic penetrating keratoplasty (TPK) and loss of anatomical integrity of globe as phthisis bulbi. Functional success was considered preservation of visual function with best corrected visual acuity (BCVA).

Results: A total of sixty seven eyes of sixty seven patients were reviewed in the present study. The mean age of all the patients was 46.63 ±16.30 years (range: 5-81 years) with predominance of males 41(61.19%). Infective keratitis (IK) constituted major chunk of aetiology for corneal perforations 44(65.67%) with maximum 47(70.14%) of size of ≥1.5-3.0mm. 56(83.58%) cases sealed completely, rest 11(16.41%) cases failed to seal. Morphological outcome showed significant relationship with age, number of glue applications and complications with P value (0.05, 0.00, 0.00) respectively. The functional outcome showed significant relationship with age, frequency of applications, morphological outcome and complications (p value 0.02, 0.00, 0.00, 0.00) respectively.

Conclusions: Infective keratitis is major cause of corneal perforations. Corneal perforations ≤3.0mm size shows healing and subsequent closure in 83.58%. Morphological and functional outcome shows significant relationship with age, number of glue applications and complications.

Key words: Infective keratitis, Corneal perforation, Tissue adhesive.

Financial Interest: Nil
Conflict of Interest: Nil
Received: 26.07.2019 Accepted: 13.11.2019

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Introduction

Corneal perforation is a cause of major ocular morbidity with profound loss of vision (Boruchoff SA et al. 1975). Etiologies of corneal perforation can be labelled as infectious, non-infectious and traumatic. It

accounts for majority in developing countries as compared to developed countries where the prevalence is very low (Panda A et al. 1995). Infective keratitis (IK) if become non-responsive to medical therapy lead to corneal melting and subsequent perforation. Haemophilus aegyptius, Corynebacterium diphtheriae, Neisseria gonorrhoeae, Neisseria meningitidis, Shigella and Listeria species can penetrate intact epithelium (McLeod SD et al, 2008). IK lead to alterations in the epithelial basement membrane which may cause persistent epithelial defect(PED). Altered epithelial cells and polymorphonuclear cells (PMC's) leads to stromal melting by proteolytic enzymes (Gundersen et al 1969). Descemet's membrane (DM) act as an effective barrier to microorganisms but it bulges forward, forming a descemetocele when stroma melts due to altered stromal collagen. Early diagnosis and timely intervention can reduce the ocular morbidity by minimizing peripheral anterior synechiae (PAS), risk of cataract formation and intraocular infection.

Achievement of best wound integrity is an important goal in ophthalmic surgery and suturing is the conventional method which is time consuming and provides discomfort. So switching to suture less surgery is need of the hour. Tissue adhesives (TA's) are group of synthetic or naturally occurring compounds, which helps in wound reconstruction either intra and post-operative (Panda A et al 2009). Cyanoacrylate glue and fibrin glue (FG) have emerged as attractive alternatives to sutures. TA's reduces inflammation, surgical time and enhance post- operative comfort without compromising wound strength. Cyanoacrylate glue and fibrin glue (FG) have come up as attractive alternatives to sutures. TA's reduces overall surgical time as well as inflammation thereby improving post-operative comfort without compromising wound strength. It should be bio-compatible, clear enough to permit vision, accessible, affordable, non-inflammatory, non-infectious and disappear eventually to permit healing at the interface. Cyanoacrylate TA's and FG both are effective for corneal perforations of size of 3 mm (Sii F et al 2005).

Keeping that in view this study was planned to evaluate the efficacy of N- butyl cyanoacrylate TA in corneal perforations in terms of morphological as well as functional outcome.

Materials and methods

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. It was a retrospective and observational case series. Data of corneal perforations in which glue was applied were reviewed retrospectively from January 2015 to April 2018.

Inclusion criteria

All corneal perforations of size ≤3.0mm within 6mm radius from central apex of cornea (Rush SW & Rush RB 2016) and perforated grafts (Post OPK, Post TPK) were studied.

Exclusion criteria

Perforations with scleral involvement, larger than 3.0mm, associated endophthalmitis or panophthalmitis and patients with follow-up period of less than three months were not studied.

Data analyzed included the age, sex, organisms causing infective keratitis, size, location of perforation, number of applications of glue, stay of glue, outcome of TA (sealed/ non-sealed), morphological and functional outcome and complications of TA application if any. The patients were divided into two age groups as ≤40 and >40 years as group 1 and 2 respectively.

Application of TA

TA was applied in the operating theater under topical anesthesia. The N-Butylcyanoacrylate

TA (Endocryl glue; SAMARTH LIFE SCIENCES PVT LTD, Himachal Pradesh) was applied. Anterior chamber intervention including air or fluid paracentesis was performed for corneal perforation with iris prolapse.

Process of application

The mode of application of cyanoacrylate varies depending on surgeon's preference. A standard technique was used to apply TA to the site of perforation (Erdey RA et al 1991). Topical anaesthesia was employed depending upon perceived patient compliance. A wire speculum was used to expose the cornea under operating microscope. Necrotic tissue and surrounding loose epithelium at site of perforation was scraped under magnification with a combination of blunt scrapping and peeling with fine forceps. Scrapings were sent for Gram's staining, KOH staining, bacterial culture and fungal culture. If no bacteria or fungus seen were considered sterile ulcers, but no case of peripheral ulcerative keratitis was included in this study. The perforation site and surrounding area was kept dry with sponges, but a thin fluid film was left in bed of perforation to avoid the entry of TA into the anterior chamber.If the anterior chamber was flat, or if there was prolapse of iris, a paracentesis was performed, and air/balanced salt solution was injected into the anterior chamber. 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. It can also be applied by using special applicator. The adhesive was allowed to air dry. Seidel's test was repeated after adhesive application. A positive Seidel's test indicating persistent leak merited immediate reapplication of TA.

In eyes where clinical judgements indicated firmer adhesion of partially prolapsed Iris tissue to the perforation edge, an air bubble was introduced through a separate stab incision before application. Bandage contact lens was applied after drying up of the TA in all the cases.

Criteria of success of TA application included resolution of infiltrates, vascularisation around site of perforation and corneal scarring or opacity. Each eye was documented for progression or reduction in symptoms, signs such as conjunctival congestion and anterior chamber reaction or uveitis. Worsening infiltrates, loss of chamber even after repeated adhesive application or enlargement of perforation size to >3.0 mm were considered treatment failures or non-sealed. Such patients subsequently required TPK. The final criteria for outcome of TA in corneal perforation was considered as sealed or non-sealed .The post TA application outcomes were collected over a period of three months as sealed or non sealed corneal perforation. Morphological outcome was considered as corneal scarring (Figure 1), required TPK and loss of eye anatomical integrity of globe as phthisis bulbi. Post operative best corrected visual acuity (BCVA) at last follow up, intraocular pressure (IOP) and complications of TA were noted. BCVA was recorded as>20/60, 20- 60-20/200, <20/200-20/400, <20/400 and denied perception of light and BCVA at last follow up was considered as functional outcome. Snellen's acuity was converted into log-MAR for statistical analysis. . Functional success[9] was defined as BCVA ranging from perception of light (PL), accurate projection of rays (PR) to>20/60 (Sharma N et al 2014).Various complications after TA application were noted during various follow up at first post operative day, two weeks, one and three months. All patients operated by single surgeon were included in the study to rule out the surgical bias.

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

if required to lower IOP. Oral acyclovir400 mg five times a day for initial two weeks if required was given. The TA remained in situ until it sloughed spontaneously after healing of perforation or required definitive surgical intervention in the form of TPK.

Statistical analysis

Data entry was done on excel spreadsheet and then SPSS software (Statistical Package for Social Sciences, version 22, SPSS Inc, Chicago, IL) was used for analysis. Statistical data were expressed in terms of means ± standard deviations (mean ± SD). The frequency and percentage was expressed for descriptive statistics. Pearson Chi- square test (Fisher exact test 2 tailed) was used to find out the association between categorical variables and outcome (sealed or non-sealed), morphological and functional outcome of application of glue in corneal perforation. Comparison of BCVA before and after glue application was carried out by using Paired T test. P value < 0.05 was considered statistically significant.

Results

Sixty seven eyes of sixty seven patients were reviewed in the present study. The mean age of included patients was 46.63 ±16.30 years (range: 5–81 years).In this study males were maximum 41(61.19%). Right eye was involved in maximum patients 36(53.73%).

Characteristics of corneal perforations

IK constituted major chunk of aetiology for corneal perforations 44(65.67%). Out of which 17(38.63%) cases were found to be fungal, 25(56.81%) cases were bacterial (grams positive) and 2(4.54%) were of viral etiology clinically who actually suffered from herpes zoster ophthalmicus (Figure 2). Maximum 47(70.14%) corneal perforations were of size of ≥1.5-3.0mm. Seidel's test was observed as positive in 34(50.74%) of cases. 34(50.74%) of corneal perforations were paracentral in location. 48(71.64%) cases had one week old symptoms. Maximum cases 52(77.61%) got glue application only once and in maximum cases 48(71.64%) glue stayed or sloughed out in <30 days with mean duration of stay of glue 24.25 ±7.14 days. 15(22.38%) patients required glue application twice because of recurrent leak or glue dislodgement. In only four cases the glue was removed to look for the perforation, but all of them were healed completely. In these cases glue actually overstayed for more than sixty days. No case of any secondary corneal infection was observed due to overstay. On the

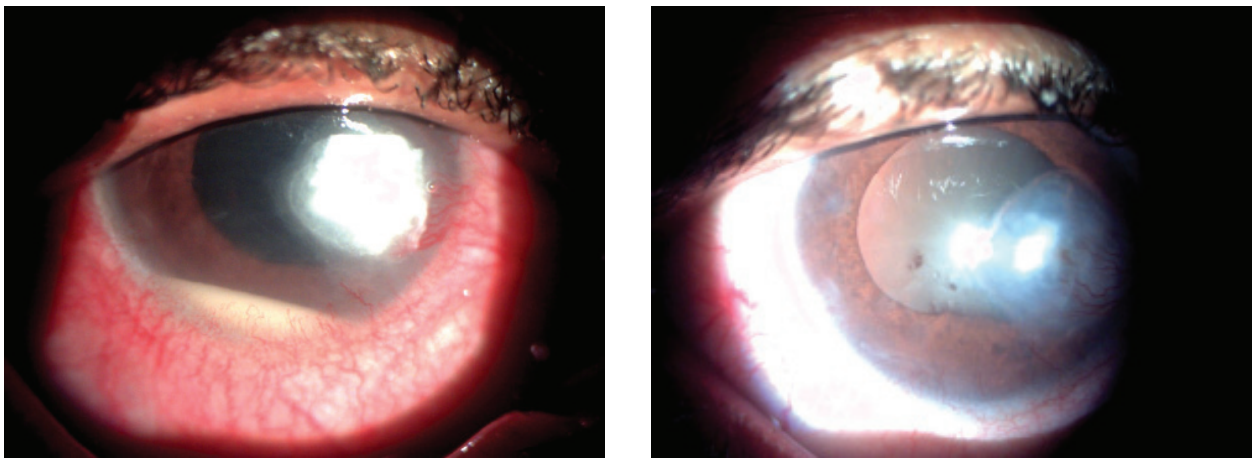

Figure 1: a) Cyanoacrylate glue applied for perforated corneal ulcer with hypopyon
b) Same eye showing healed perforation with vascularised corneal opacity (morphological outcome)

contrary these healed corneas showed heavy superficial and deep vascularization. No case of endophthalmitis was reported in this study despite the fact there were two aphakic patients with microbiologically proven bacterial keratitis.

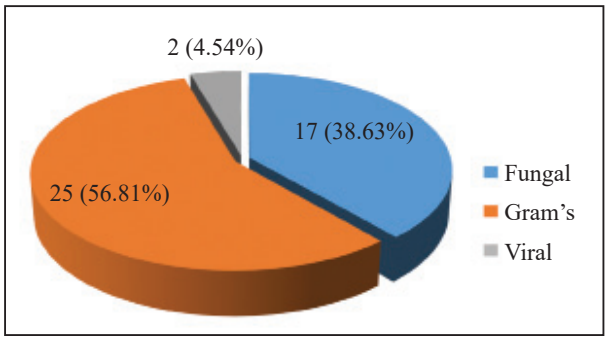

Figure 2: Pie chart demonstrating various types of infective keratitis

Table 1: Depicting the demographic and various baseline characteristics

Age(years)	
≤40	26(38.8)
>40	41(61.2)
Gender n(%)	
Male	41(61.19)
Female	26(38.80)
Etiology	
Infective keratitis	44(65.67)
Trauma	3(4.47)
Graft infection	4(5.97)
Sterile	14(20.89)
Chemical burns	2(2.98)
Size of perforation(mm)	
<1.5	20(29.85)
≥1.5-3.0	47(70.14)
Seidel's test	
Positive	34(50.74)
Negative	33(49.25)
Location of perforation	
Central	
Paracentral	33(49.25)
Duration of symptoms	34(50.74)
<1 week	
≥1 week	19(28.35)
Number of glue applications	48(71.64)
Once	
Twice	52(77.61)
Stay of glue(days)	15(22.38)
<30	
≥30	48(71.64)
Outcome of tissue adhesive	19(28.35)
Sealed	
Not sealed	56(83.58)
Overall Morphological outcome	11(16.41)
Corneal scarring(opacity)	
Yes	42(62.68)
No	11(16.41)
Needed TPK	10(14.92)
Phthisis bulbi	4(5.97)
Functional outcome	
BCVA	
>20/60	12(17.91)
20-60-20/200	32(47.76)
<20/200-20/400	0
<20/400	18(26.86)
PL denied	5(7.46)
Complications of tissue adhesive	6(8.95)
Corneal melt	13(19.40)
Cataract	6(8.95)
Uveitis	2(2.98)
Glaucoma	1(1.49)
Phthisis	39(58.20)
None	

BCVA: Best corrected visual acuity

Table 2: At presentation and final BCVA

BCVA	At presentation	At last follow up
>20/60	3(4.47)	12(17.91)
20-60-20/200	13(19.40)	32(47.76)
<20/200-20/400	0	0
<20/400	49(73.13)	18(26.86)
PL denied	2(2.98)	5(7.46)

BCVA: Best corrected visual acuity

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

	Morphological outcome				
Variables	**Corneal opacity N(%)**	**TPK N(%)**	**Phthisical N(%)**	**Transparent cornea N(%)**	**P* value**
Age(years)					
≤40	11(26.2)	3(30.0)	2(50)	10((90.9)	
>40	31(73.8)	7(70)	2(50)	1(9.1)	0.00
Etiology					
Infective keratitis	29(69)	6(60)	1(25)	8(72.7)	
Trauma	2(4.8)	0	0	1(9.1)	
Graft infection	3(7.1)	0	1(25)	0	
Sterile	7(16.7)	3(30)	2(50)	2(18.2)	
Burns	1(2.4)	1(10)	0	0	0.55
Size of perforation					
<1.5	10(23.8)	4(40)	1(25)	5(45.5)	0.46
≥1.5-3.0	32(76.2)	6(60)	3(75)	6(54.5)	
Location of perforation					
Central	20(47.6)	4(40)	1(25)	8(72.7)	
Paracentral	22(52.4)	6(60)	3(75)	3(27.3)	0.28
Duration of symptoms					
<1 week	9(21.4)	2(20)	2(50)	6(54.5)	0.11
≥1 week	33(78.6)	8(80)	2(50)	5(45.5)	
Number of glue applications					
Once	33(78.6)	5(50)	4(100)	10(90.9)	
Twice	9(21.4)	5(50)	0	1(9.1)	0.05
Stay of glue(days)					
<30	29(69)	8(80)	3(75)	8(72.7)	0.91
≥30	13(31)	2(20)	1(25)	3(27.3)	
Complications					
Corneal melt	0	6(60)	0	0	
Cataract	10(23.8)	1(10)	0	2(18.2)	
Uveitis	5(11.9)	0	0	1(9.1)	
Glaucoma	1(2.4)	1(10)	0	0	
Phthisis	0	0	1(25)	0	
None	26(61.9)	2(20)	3(75)	8(72.7)	0.00

P* value calculated by Pearson Chi-square test (Fisher exact test) two tailed

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

Variables	Functional outcome					
	>20/60 N(%)	20-60-20/200 N(%)	<20/200-20/400 N(%)	<20/400 N(%)	PL denied	P# value
Age(years)						
≤40	9(75)	8(25)	0	7(38.9)	2(40)	
>40	3(25)	24(75)	0	11(61.1)	3(60)	0.02
Etiology						
Infective keratitis	9(75)	24(75)	0	10(55.6)	1(20)	
Trauma	1(8.3)	2(6.3)	0	0	0	
Graft infection	0	1(3.1)	0	2(11.1)	1(20)	
Sterile	2(16.7)	5(15.6)	0	4(22.2)	3(60)	
Burns	0	0	0	2(11.1)	0	0.13
Size of perforation						
<1.5	6(50)	9(28.1)	0	3(16.7)	2(40)	
≥1.5-3.0	6(50)	23(71.9)	0	15(83.3)	3(60)	0.25
Location of perforation						
Central	(58.3)	15(46.9)	0	10(55.6)	1(20)	
Paracentral	5(41.7)	17(53.1)	0	8(44.4)	4(80)	0.48
Duration of symptoms						
<1 week	5(41.7)	7(21.9)	0	5(27.8)	2(40)	
≥1 week	7(58.3)	25(78.1)	0	13(72.2)	3(60)	0.56
Number of glue applications						
Once	11(91.7)	27(84.4)	0	9(50)	5(100)	
Twice	1(8.3)	5(15.6)	0	9(50)	0	0.00
Stay of glue(days)						
<30	10(83.3)	20(62.5)	0	15(83.3)	3(60)	
≥30	2(16.7)	12(37.5)	0	3(16.7)	2(40)	0.30
Overall morphological outcome						
Corneal scarring(opacity)						
Yes	3(25)	27(84.4)	0	11(61.1)	1(20)	
No	0	3(9.4)	0	7(38.9)	0	
Needed TPK	0	0	0	0	4(80)	
Phthisis bulbi	9(75)	2(6.3)	0	0	0	0.00
Complications						
Corneal melt	0	2(6.3)	0	4(22.2)	0	
Cataract	0	9(28.1)	0	4(22.2)	0	
Uveitis	2(16.7)	4(12.5)	0	0	0	
Glaucoma	0	0	0	2(11.1)	0	
Phthisis	0	0	0	0	1(20)	
None	10(83.3)	17(53.1)	0	8(44.4)	4(80)	0.00

P# value calculated by Pearson Chi-square test (Fisher exact test) two tailed

Morphological outcome

A total of 42(62.68%) cases healed by corneal scarring or opacity formation and among all these cases corneal vascularization was observed. 10(14.92%) cases underwent TPK and 11(16.41%) cases had no opacification of cornea and all these cases were having size of perforation <1.5mm. 4(5.97%) cases went into phthisis bulbi or lost its anatomical integrity after glue application out of which one was non-sealed and two were sealed and one case got reinfection after TPK and eventually went phthisical shown in table- I. Morphological outcome showed significant relationship with age, number of glue applications and complications with P value (0.00,0.05,0.00) respectively which is described in table- III.

Functional outcome

At presentation maximum patients 49(73.13%) had BCVA <20/400 and at last follow up maximum patients 32(47.76%) could get the BCVA in between 20/60-20/200. 5(7.46%) patients were denied perception of light (PL) at last follow up out of which two patients were PL denied at time of presentation. The functional outcome showed significant relationship with age, number of glue applications, morphological outcome and complications with P value (0.02, 0.00, 0.00, 0.00) respectively which is described in table- IV. There was significant difference between the pre and post glue BCVA with Mean±SD (0.67±0.08) with P value = 0.00 which is explained in table- II.

Complications of TA

Cataract was seen in 13(19.40%) cases and all these cases were those who showed Seidel's test positive with flat anterior chamber at time of presentation.Corneal melting was observed in 6(8.95%) of cases despite twice glue application and all these cases underwent TPK eventually. One case got phthisical globe as that case was aphakic and vitreous herniation was seen through the perforation. Despite glue application for two times, it could not heal but went phthisical which is shown in table- I.

Discussion

TA is the standard management for small impending or manifest corneal perforations up to 3-mm because of its adhesive strength and polymerization rate (Vote BJT et al 2000). It stays at wound site for a longer duration due to its non-biodegradability. It has antibacterial properties and arrests the progression of keratolysis (Setlik DE et al 2005).

TA is used as a temporary measure to provide the tectonic support to the tissue to make PK pending which eventually can be the definitive therapy. Large corneal perforations if not addressed well in time can lead to disastrous complications of endophthalmitis, panophthalmitis and loss of eye ultimately. Perforated corneal ulcers constitutes the major indication for TPK (Raj A et al 2018).

In the present study major etiology of perforated corneal ulcers was IK to the tune of 65.67% in contrast to conclusions of study by (Lekskul et al 2000) who reported Keratoconjunctivitis sicca as the most common underlying disease associated with non-traumatic corneal perforation.

In this study maximum 61.19% patients involved were males and the predominance of males was comparable with the results of another study which showed male preponderance of 84.6% (Prakash et al. 2012). The trend of predominance of males for IK and TPK in the developing world could be attributed to various socioeconomic factors, more susceptibility to trauma and their easy accessibility to hospitals (Raj A et al. 2018). Hirst et al (1983) have reported lower enucleation rate and better visual results after application of TA in corneal perforations. Leahey et al. (1993) 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 this study in perforation ≤3.0mm in size. 70.14% of perforations in this study were ≤1.5-3.0mm. 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 (2000) 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 is in accordance with the present study in which 83.58% were sealed. Garg et al. (2003) reported corneal scarring in cases of TA application in cases of fungal keratitis to the tune of 63.3% which is nearly the same to the current study where healing occurred by corneal opacification in 62.68% of cases.

In the present study various outcomes of corneal gluing were analyzed in reference to morphological and functional outcome. It was found that 83.58% perforations were sealed with glue application and 62.68% showed corneal scarring or opacification. In 14.92% cases TA failed to seal the perforation and required TPK. Garg et al. (2003) reported that 25(34.2%) of cases with fungal keratitis cases required multiple applications which is in concordance with current study where 22.38% cases required twice TA application because it dislodged without healing.

The duration of symptoms, size and location of perforation does not show significant relation with outcome or sealing of perforations which is in concordance to observations by (Garg et al 2003) who reported that the duration of complaints, indication of application, and the type of fungal isolate did not affect the outcome in these cases. TA was removed at the time of surgery or allowed the glue to dislodge spontaneously when the epithelization under the glue was complete. TA remained or stayed for a mean 24.25 ±7.14 days. In the present study in 28.35% cases it stayed for > 30 days and all these cases healed which shows consistency with the observation reported by (Garg et al. 2003) who reported that the infiltrate ultimately resolved in cases where the adhesive had been left on the cornea for more than one month.

Conclusion

Major cause of corneal perforations is IK. Corneal perforations ≤3.0mm in size shows sealing in 83.58%. Morphological outcome depends upon age, number of applications of glue and complications significantly. Functional outcome of tissue adhesive shows significant association with age, number of applications of glue, morphological outcome and complications significantly.

Acknowledgement: Mr. Shubham Pandey, Assistant Professor and Head, biostatistics department; Mr Ankit, Lecturer, department of biostatistics for statistical analysis, Mr. Surendra Singh Bhandari, office assistant for technical support and

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