Original Article

Intracorneal scleral patch supported cyanoacrylate application for corneal perforations secondary to rheumatoid arthritis

Ashok Sharma, Rajan Sharma, Verinder S Nirankari[1]

Purpose: To describe a new technique of intracorneal scleral patch (ICSP) supported cyanoacrylate tissue adhesive (CTA) application in corneal perforations, greater than 3.0 mm secondary to rheumatoid arthritis (RA). **Methods:** This Prospective, non-randomized, non-comparative, interventional series included 14 eyes (14 patients). All patients had corneal perforations sized 3.5 to 4.5 mm due to RA, which were treated with ICSP supported CTA application. A partial thickness scleral patch 1.0 mm larger than diameter of corneal perforation was prepared. A lamellar corneal pocket 0.5 mm all around the corneal perforation was created. The partial thickness scleral patch was placed in the corneal perforation site and the edge was fitted into the lamellar intracorneal pocket. A minimum quantity of CTA was applied on the scleral patch to seal the perforation. **Results:** The corneal perforations healed in 14 eyes (100%) in a mean 7.71 ± 1.14 (range, 6–9) weeks. One eye (7.14%) had inadvertent extrusion of ICSP due to premature removal of CTA but, Seidel's test was negative, and the corneal epithelial defect healed with BCL alone. One eye each (7.14%) developed steroid induced cataract and glaucoma. None of eyes developed infective keratitis, re-opening of corneal perforation (necessitating repeat procedure) or enlargement of corneal perforation requiring penetrating keratoplasty (PKP). **Conclusion:** ICSP supported CTA application is a successful alternative option to emergency PKP in treating corneal perforations sized 3.5 to 4.5 mm with associated RA.

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Website: www.ijo.in

DOI: 10.4103/ijo.IJO_2258_19

Quick Response Code:

Key words: Corneal perforation, cyanoacrylate tissue adhesive, rheumatoid arthritis, scleral patch, Stevens-Johnson syndrome

The occurrence of perforation in corneal disease is a serious complication. It threatens visual potential and requires an urgent management. Size of the corneal perforation determines the suitability of treatment option.[1,2] Corneal perforations up to 3.0 mm are amenable to the CTA or fibrin glue (FG) application alone.[3-6] Most corneal surgeons favor tectonic penetrating keratoplasty (TPKP) or deep anterior lamellar keratoplasty (DALK) for corneal perforations larger than 3.0 mm.[7-10] However both TPKP and DALK are surgical procedures require technical expertise and donor cornea. Results of TPKP and DALK in corneal perforations associated with RA are less favorable.[11,12]

Several authors favor the use of tissue scaffolds to assist CTA and FG application.[13-15] In a recent publication, scleral patch augmented CTA application has been used to treat moderate sized corneal perforations (3.5 to 4.5 mm) successfully.[15] In this study the authors placed partial thickness scleral patch at the site of corneal perforation and then applied CTA to seal the corneal perforation. Amniotic membrane graft (AMG), autologous Tenon's capsule and optical/non- optical grade of cornea have also been used as scaffolds.[13-15]

In a retrospective study, CTA application was found effective in healing only one third corneal perforations due to herpes simplex keratitis (HSK).[16] Corneal perforations associated with RA also respond less favorably to CTA application alone. In patients with moderate sized (3.5 to 4.5 mm) corneal perforations due to RA, we placed a partial thickness scleral patch in the intracorneal lamellar pocket and applied CTA. We present results of 14 cases treated with this technique.

Methods

This prospective, interventional, non-comparative study included fourteen patients (14 eyes), clinically diagnosed to have corneal perforation associated with RA. This study was approved by the Institutional Review Board. The study was conducted with adherence to the tenets of the Declaration of Helsinki. All patients underwent complete ophthalmic examination including recording of history, treatment details, and history suggestive of any systemic disease. Corneal perforation was diagnosed in the presence of extreme corneal thinning, shallow anterior chamber and iris presenting at the site of corneal thinning. The clinical diagnosis of corneal perforation was confirmed by performing Seidel's test. Patients with corneal perforation and infiltrate were subjected to

Cornea Service, Chandigarh, India, [1]Cornea Service, Katzen Eye Group, Owings Mills, MD, USA

Correspondence to: Dr. Ashok Sharma, Dr Ashok Sharma's Cornea Centre, SCO 2463-2464, Sector 22C, Chandigarh - 160 022, India. E-mail: asharmapgius@yahoo.com

Received: 09-Dec-2019 Revision: 06-Mar-2020
Accepted: 06-Jun-2020 Published: 15-Dec-2020

Cite this article as: Sharma A, Sharma R, Nirankari VS. Intracorneal scleral patch supported cyanoacrylate application for corneal perforations secondary to rheumatoid arthritis. Indian J Ophthalmol 2021;69:69-73.

detailed microbiological tests including corneal scraping for Gram stain, KOH wet mount and culture on various media. All patients underwent complete blood count, ESR, RF, ANA, CRP, ANCA, and hepatitis C. Fourteen patients with negative microbiological tests and positive immunological tests for RA were included.

Patients with corneal perforations up to 3.0 mm and those with primary infective aetiology were excluded. Five patients with moderate sized (3.5–4.5 mm) corneal perforations, post HSK (3) and post bacterial keratitis (2) were also not included. Patients having corneal perforations larger than 4.5 mm were also excluded.

Re-application of CTA was considered in case CTA adhesive plug got displaced and Seidel's test was still positive. In patients with negative Seidel test only BCL was placed. Repeat procedure (ISCP supported CTA application) was considered if ICSP and CTA plug both got dislodged. Healing was defined as closure of corneal perforation, negative Seidel test and re-epithelialization of corneal wound.

Surgical procedure

All procedures were performed in the operating room. Prior informed consent was obtained from each patient. The surgical procedure of ICSP supported CTA application was performed under low dose, 5.0 ml; 2.5 ml each of lignocaine hydrochloride 2% inj. (Lox 20 mg/ml Neon Laboratories, India) and Bupivacaine hydrochloride 0.5% (Bupitroy 5 mg/ml Troikaa Pharamaceutical Ltd India) peribulbar anesthesia. The corneal perforation was cleaned and debris present over the iris and perforation site was removed. The corneal epithelium surrounding the corneal perforation and ulcerating stroma was removed. Adhesions between the iris and the margin of the corneal perforation were lysed using blunt tipped canula. Iris was pushed back into the anterior chamber. Intracorneal pocket 0.50 mm around the perforation at about 50% depth of the cornea was created using crescent knife. Donor sclera was obtained from local eye bank, screened, harvested and prepared using standard eye banking procedure.[15] Donor sclera was taken out and was placed in the normal saline for 15 minutes to leach out glycerine. Then, the tissue was placed into the solution containing amikacin sulphate 2% (Alfakim 500 mg/2 ml Ranbaxy India) and vancomycin hydrochloride 5% (Vanking 500 mg/vial Neon Laboratories India) for 5 minutes. The size of the corneal perforation was measured with Castroviejo calipers. The scleral patch 1.0 mm larger than the size of corneal perforation was punched out with appropriate-sized skin biopsy punch from the glycerine preserved sclera. The scleral patch was then dissected in a lamellar fashion with crescent knife to obtain sclera patch of approximately 1/3 of original thickness. This partial thickness scleral patch was placed in the intra corneal pocket. The surface of scleral patch, edge of the corneal perforation and surrounding corneal surface was dried using Weck-Cel ophthalmic sponge. Isoamyl 2-cyanoacrylate (Amcrylate; Concord Drugs Ltd, Hayathnagar, Andhra Pradesh, India) was drawn into a 2 ml disposable syringe with 26-gauge needle. A minimal amount of CTA was applied on the ICSP surface and margin of corneal perforation. CTA was allowed to polymerize and adhesive mass became visible. The anterior chamber was filled with balanced salt solution. An air bubble was placed in eyes with shallow anterior chamber. Finally, a BCL was placed. Diagrammatic illustration of surgical procedure [Fig. 1] and actual steps [Fig. 2a-d] have been added. The video of the surgical procedure has been added as SDC file [Video 1].

Postoperative treatment included instillations of moxifloxacin 0.5% (Vigamox 5 mg/ml; Alcon Laboratories, USA, Inc.), prednisolone acetate 1% suspension (Pred Forte, 10 mg/ml Allergan USA, Inc.), cyclopentolate hydrochloride 1% (Cyclate 10 mg/ml ZydusCadila Healthcare Ltd, India) and sodium carboxymethyl cellulose1% (Refresh Liquigel 10 mg/ml Allergan USA, Inc.) each thrice daily. All patients received Tab Prednisolone 1 mg/KBW for 3 weeks and then tapered gradually. All patients were treated by rheumatologist for systemic disease and were monitored for disease activity and dose of immunosuppressive agents, oral methotrexate (7.5–15 mg weekly dose), chloroquine (4 mg/kbw per day). Treatment of dry eye including sodium carboxymethyl cellulose 1% (RefreshLiquigel 10 mg/Ml Allergan USA, Inc.) every 2 hours and cyclosporine ophthalmic emulsion 0.05% (Restasis 0.5 mg/Ml Allergan USA, Inc.) twice daily were continued.

Results

Fourteen patients (14 eyes) had corneal perforations (3.5–4.5 mm) due to RA and were treated with ICSP supported CTA application treatment. The mean age of 14 patients (6 men and 8 women) was 56.7 ± 13.3 years (range, 29–73 years). The aetiology of corneal perforations were RA in 13 (92.9%), combined RA and Stevens-Johnson syndrome (SJS) in 1 (7.1%) patients. All patients had severe dry eye. The mean diameter of the corneal perforations was 3.93 ± 0.43 mm (range, 3.5–4.5 mm). Ten (71.4%) patients had peripheral corneal perforations and 4 (28.6%) central perforations [Table 1].

All 14 patients underwent ICSP supported CTA application. None of the eyes required any 10-0 nylon suture. Corneal perforations healed in 14 (100%) eyes resulting in corneal opacities. The mean time for re-epithelialization was 7.71 ± 1.14 weeks (range, 6–9 weeks) [Table 1]. One patient with a peripheral perforation (7.14%) had inadvertent extrusion of ICSP due to early (at 4 weeks) removal of CTA plug [Fig. 3a and b]. The dislodgement of scleral patch graft

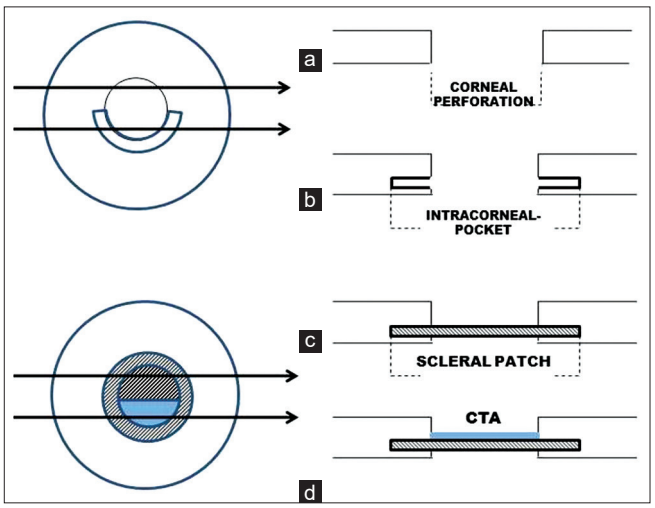

Figure 1: Schematic representation of ICSP CTA technique. (a) Corneal perforation. (b) Lamellar corneal pocket. (c) Partial thickness scleral flap in the lamellar corneal pocket. (d) CTA application on the ICSP at edge of perforation

Table 1: Demographics, clinical profile, complications and outcome following intra corneal sclera patch augmented CTA application

Pt No	Age/ Sex	Etio	Perf (mm)	Location	ICSP	Comp	Add proc	Heal corn op	Heal time wks	PKP/ TPK	Pre BSVA	Post BSVA	Follow up (mo)
1	68F	RA	3.50	P	ICSP	Cat	nil	yes	7	nil	0.40	0.78	15
2	72M	RA	4.50	C	ICSP	nil	nil	yes	9	nil	1.78	1.78	13
3	49M	RA	4.00	P	ICSP	nil	nil	yes	8	nil	1.00	0.78	18
4	56M	RA	3.50	P	ICSP	nil	nil	yes	7	nil	0.78	0.60	24
5	36M	RA	3.50	P	ICSP	Cos	nil	yes	8	nil	0.30	0.30	17
6	73F	RA	4.50	C	ICSP	nil	PP	Yes	9	nil	1.30	1.30	22
7	58F	RA	4.00	P	ICSP	nil	PP	Yes	6	nil	0.40	0.40	09
8	29F	RA*	3.50	P	ICSP	nil	nil	yes	7	nil	0.78	1.00	12
9	61F	RA	4.50	C	ICSP	nil	PP	yes	9	nil	1.30	1.30	14
10	46F	RA	3.50	P	ICSP	nil	nil	yes	7	nil	1.0	1.00	21
11	57M	RA	3.50	P	ICSP	Ina Ext	BCL	yes	9	nil	1.0	1.0	26
12	69F	RA	4.00	C	ICSP	nil	nil	yes	7	nil	1.30	1.30	16
13	53M	RA	4.50	P	ICSP	nil	nil	yes	6	nil	1.0	0.78	11
14	67F	RA	4.0	P	ICSP	St Gl	nil	Yes	9	nil	0.78	0.60	15

Pt=Patient, M=Male, F=Female, Etio=Etiology, RA=Rheumatoid arthritis, RA*=Rheumatoid arthritis and Steven's Johnson Syndrome, Perf=Corneal perforation, P=Peripheral, C=Central, ICSP=Intra corneal sclera patch, Comp=Complication, Cat=Cataract, Cos=Cosmetic issue, Ina Ext=Inadvertent extrusion, St Gl=Steroid glaucoma, Add proc=Additional procedure, Corn op=Corneal opacity, wks=Weeks, PKP=Penetrating keratoplasty, TPK=Tectonic penetrating keratoplasty, BSVA=Best corrected visual acuity

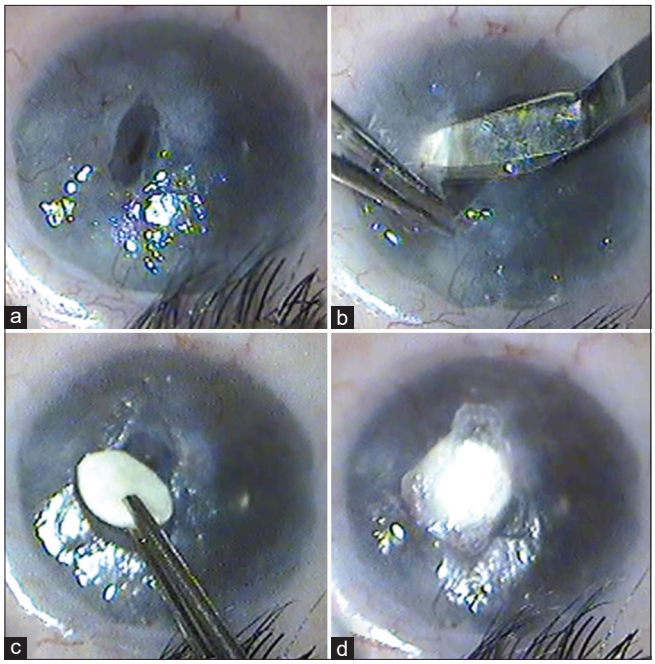

Figure 2: *In vivo* steps of ICSP CTA technique. (a) Pre- treatment corneal perforation (3.5 mm). (b) Creation of lamellar corneal pocket using crescent knife. (c) Partial thickness scleral flap being inserted into the lamellar corneal pocket. (d) CTA applied on the ICSP at edge of perforation

occurred as the CTA plug was firmly adhered to sclera patch and the removal was tried without waiting for CTA plug to become loose. The inadvertent extrusion left a corneal epithelial defect and the Seidel's test was negative [Fig. 3c]. A bandage contact lens was placed and the corneal epithelial defect healed in 2 weeks. One eye (7.14%) developed cataract and one eye (7.14%) developed steroid induced glaucoma.

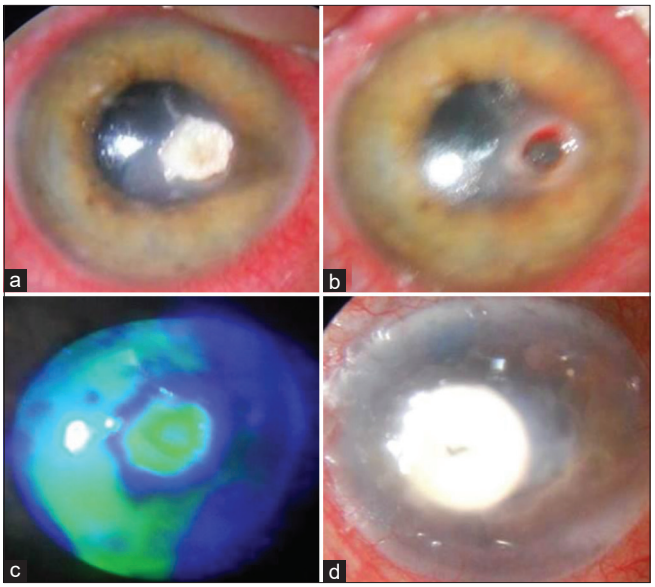

Figure 3: Complications of ICSP CTA technique. (a) Sealed corneal perforation 6 weeks post ICSP CTA application. (b) Inadvertent extrusion of scleral patch at the time of removal of CTA. (c) Negative Seidel's test, treated with BCL. (d) Cosmesisissue in patientwith healed corneal perforation (4.5 mm) at 18 weeks follow-up

Another patient (7.14%) showed concern about the cosmesis at 18 weeks [Fig. 3d]. Two eyes (14.28%) underwent punctal plugs insertion and one (7.14%) bandage contact lens application after intracorneal sclera patch supported CTA application. None of the eyes required additional surgical treatment including TPKP for healing of the corneal perforation.

The overall mean follow-up of the patients was 15.5 ± 3.32 months (range, 10–21 months). The mean logMar BCVA in these 14 eyes was 0.92 ± 0.40 at the last follow-up [Table 1]. One

patient (7.14%) had combined RA and SJS, developed paracentral corneal melt at different location 6 months after healing of the corneal perforation. The patient had discontinued systemic treatment. The patient was put on systemic corticosteroid and immunosuppressive treatment (Methotrexate 15 mg per week). The corneal melt improved in 3 weeks. No patient developed infectious keratitis, increased intraocular inflammation, CTA penetration into the anterior chamber, endophthalmitis, choroidal detachment, or fibrous ingrowth. None of the patients required enucleation.

Discussion

ICSP supported CTA application is an effective option for treatment of corneal perforations (3.5–4.5 mm) due to RA. Since the edge of the partial thickness scleral patch occupies the lamellar corneal pocket, the corneal perforation heals very well. Combined RA and SJS as underlying cause of severe dry eye and corneal perforation is a rare and worst case scenario. In one such case we had successful outcome with ICSP supported CTA application while CTA application alone had been unsuccessful.

Corneal glue application is considered a standard of care for the treatment of corneal perforations upto 3.0 mm diameter. Upon coming in contact with OH^- ions, CTA polymerizes and forms a solid adhesive plug and seals the corneal perforation. However, in corneal perforations larger than 3.0 mm, there is a risk of inadvertent intracameral access and iris touch of CTA. This can be prevented by a newer concept of tissue scaffold assisted CTA application as it acts as a barrier. Several tissues including AMG,[13,17,18] iris,[14] Tenons patch[19] and scleral patch[16] have been used to assist glue application.

Scleral patch graft augmented CTA application has been successfully used to treat moderate sized (3.5–4.5 mm) non-infectious corneal perforations.[16] In this published technique, the authors placed an appropriate sized partial thickness scleral patch at the site of perforation and applied CTA over the sclera patch and at the edge of the corneal perforation. This procedure may be useful for patients suffering from moderate-sized corneal perforations due to Mooren's ulcer who have significant surrounding corneal thinning. For similar sized perforations due to RA, the authors report and discuss a new innovation that uis, ICSP supported CTA application. This technique may be useful in treating moderate sized (3.5–4.5 mm) corneal perforations with no significant surrounding corneal thinning.

ICSP acts as a barrier and prevent the inadvertent access of CTA into the anterior chamber. Intraocular penetration of CTA is known to cause severe inflammation. The second function, ICSP serves as a scaffold for the keratocytes to grow. Without this scaffold, fibrous tissue either takes very long time to bridge the gap or it may not be able to close it at all. In such cases, the corneal perforation may be open on removal of the CTA plug. Another benefit of ICSP is that it withstands the continued collagenolysis, as the edge of the scleral patch is in the lamellar corneal pocket all around. Before selecting sclera as scaffold, we tried cornea in some of the cases. The problem we faced with the use of the corneal tissue was that on getting hydrated corneal tissue used to swell and lift the CTA adhesive plug. Thus, the corneal tissue and CTA adhesive complex used to become lose. Concomitant use of CTA seals the corneal perforation immediately. In addition, CTA along with scleral patch provides tectonic support. Partial thickness scleral patch after application of CTA on anterior surface becomes rigid and application of CTA at margin prevents extrusion of the partial thickness sclera patch. CTA has also been reported to possess anti-bacterial and anti-fungal properties.[4,20,21] CTA prevents the ingress of PMN cells into the ulcerating stroma and thus decreases the load of collagenolytic enzymes.[22] In addition to the use of topical corticosteroids, systemic steroids, and immunosuppressive drugs used as adjunct medical treatment also decreased the collagen degradation. All these mechanisms make this procedure an ideal choice for moderate sized corneal perforation associated with RA.

Medical treatment of RA is of paramount importance to arrest corneal collagenolysis and promote healing of corneal perforation. The treatment of RA includes corticosteroids, nonsteroidal anti-inflammatory drugs, and DMARDs. DMARDs may help by decreasing collagenolysis, due to inhibition of leukocyte replication and release of inflammatory mediators. DMARDs can be grouped into traditional (methotrexate, leflunomide and hydroxychloroquine) and biological group include, TNF inhibitors (infliximab, adalimumab, etanercept), T cell inhibitor (abatacept) and IL-6 inhibitor (tocilizumab).[2] Due to high cost and non-availability of some of the newer biological DMARDs, patients in this study were treated with traditional DMARDs. Azathioprine has been reported to cause endothelial damage[21] and was not used in the treatment of any of the patients included in our study. Patients who could not afford other immunosuppressants were given oral steroids.

Cyanoacrylate derivatives have been reported to exhibit cytotoxicity to human corneal epithelial cells, keratocytes and corneal endothelial cells.[22] As the length of the side chain increases the level of cytotoxicity decreases. Thus N-butyl cyanoacrylate shows lower levels of corneal cytotoxicity compared to methyl cyanoacrylate which has shorter side chain.[23] CTA derivatives with longer side chain molecules butyl, isobutyl and octyl have been used to treat corneal perforations. Of these Butyl derivatives have been used more often.[4] However, in recent studies octyl derivatives have also been used to treat corneal perforations and repair leaking filtering blebs without any adverse effect successfully.[24] Alternatively, the hydrogel derivatives have also been used to treat corneal perforation.[25,26] These compounds have been reported to induce less inflammation and vascularization. These compounds are relatively transparent and status of corneal healing may be visible through it. Clinically, we did not encounter any adverse effect of N-butyl cyanoacrylate in any of our patients.

Fibrin glue, a biological tissue adhesive is another alternate option to CTA. This is non-cytotoxic and provides growth factors which promote healing. In a comparative study, fibrin glue has been found equally effective to CTA in treatment of corneal perforations less than 3.0 mm.[4] Fibrin glue provided faster healing, lesser inflammation and lesser corneal vascularization as compared to CTA.

We did not encounter wound leak, enlargement of corneal perforation and infective keratitis in any of our patients. None of our patients required repeat procedure of ICSP supported CTA application, TPKP or TDALK. In one patient, inadvertent extrusion of scleral patch occurred while removing the CTA mass. The reason for extrusion in this patient was premature removal of CTA before it became loose. Unacceptable cosmetic appearance was a disadvantage of the procedure in some patients. Patients with central perforations may need PKP at a later date.

Conclusion

The ICSP supported CTA application is an effective therapeutic modality in treating moderate sized (3.5–4.5 mm) corneal perforations with associated RA. In our experience, the procedure also successfully healed a moderate corneal perforation in a patient with combined RA and SJS.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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