



OUTCOMES OF CONJUCTIVAL AUTOGRAFT IN THE RECONSTRUCTION OF SURGICAL OCULAR SURFACE DEFECTS USING FIBRIN GLUE, AN EIGHT YEAR FOLLOW-UP STUDY

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ABSTRACT

Importance: To assess the efficacy of conjunctival auto graft (CA) done using fibrin glue (FG) for the reconstruction of ocular surface defects caused by the excision of pterygia(recurrent), combined naevus of conjunctiva & miltoma of conjunctiva.

Objective: to study & assess the use of CA done using fibrin glue in:

- 1) Reconstructing conjunctival defects & in postoperative cosmesis, and
- 2) To find out the incidence of recurrences of the pathology & types of postoperative complications.

Design of the study: Prospective, interventional case series study, conducted from Jan 2006 to Dec 2014.

Setting: Institutional study, done at Kempegowda Institute of Medical Sciences, Bangalore.

Participants/Materials and methods: Ten eyes of nine patients who visited the outpatient department with various ocular surface disorders were selected randomly. All underwent CA done using fibrin glue (Reliseal) following surgical excision of the pathology. Eight eyes were of recurrent pterygium, one eye of malt lymphoma of size 12mm x 10mm & one case of combined naevus 8mm x 6mm. Follow up ranged from 3 to 8 years (Jan 2006 to Dec 2014).

Outcomes: All the cases showed good ocular surface reconstruction & showed no recurrences over the follow up period.

Results: Eight eyes having recurrent pterygium, satisfying the inclusion criteria underwent pterygium excision with CA using fibrin glue. One eye of malt lymphoma underwent CA with fibrin glue after total excision of the malt lymphoma, One case of combined naevus of limbus underwent total excision with CA using fibrin glue. Success was achieved in 100% of the cases with respect to prevention of recurrences & 90% with respect to cosmetic surface reconstruction.

Conclusion: CA done using fibrin glue resulted in the effective management of ocular surface defects following the excision of various conjunctival pathologies.

Keywords: conjunctival auto graft, recurrent pterygium, malt lymphoma, limbal combined naevus, fibrin glue.

INTRODUCTION

AUTOGRAFT IN RECURRENT PTERYGIA

The main complications of conjunctival surgeries are recurrence of the primary lesion, formation of

granulomas, ulcerations, symblepheron & the others include scleral melting, conjunctivitis, dellen, excessive bleeding, injury to medial rectus muscle, secondary glaucoma, iritis, corneal perforation or corneal ulcer.

The simplest technique of bare sclera excision alone in pterygium surgery proved unsatisfactory because of high recurrence rates. Youngson declared

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the pterygium recurrence rate as 37% in 100 cases with the same technique.¹ Demireller and colleagues reported 8 (42%) recurrences in 19 eyes treated by bare sclera technique.²

Adjunctive treatments to pterygium excision to reduce the recurrence rates are-

1. **Beta irradiation:** has reduced the recurrence rates to around 12%, but was associated with significant complications such as scleromalacia.³ Disfiguring skin depigmentation, cataract, severe secondary glaucoma, uveitis, corneal perforation and scleral necrosis resulting in perforation and secondary endophthalmitis.
2. **Mitomycin C:** can reduce recurrence rates but can cause severe secondary glaucoma, corneal edema, corneal perforation, corectopia, iritis, sudden onset mature cataract, scleral calcification and incapacitating photophobia and pain. The safety of mitomycin C therapy remains to be determined with future long-term trials.⁴
3. **Conjunctival autograft (CA):** is a technique which is safe & convenient procedure done either with or without inclusion of limbus & helps to prevent recurrences while covering the bare sclera. This technique is easy & free of most problems associated with the other measures to prevent recurrences. Studies have reported the effectiveness of CA in the prevention of recurrent of pterygia⁵ & also that limbal conjunctival autografts were more effective than free conjunctival autografts for treatment of recurrent pterygia ($p < 0.05$). Syam and colleagues reported a recurrence rate of 3.3% following inferior conjunctival autograft for primary pterygia in a study of 30 eyes.⁶

AUTOGRAFT TO COVER OCULAR SURFACE DEFECT CAUSED BY MALTOMA

The majority of lymphomas in ocular adnexa are low-grade B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) lymphoma.⁷ Maltomas show good response to radiotherapy but has side effects, of which the common ones are cataract formation & radiation retinopathy.⁸

Patients with primary ocular adnexal MALT lymphomas presenting with localised disease require local treatment and have a better outcome compared with patients with other types. The follow up outcomes of only local excision are comparable

to the outcomes of patients treated with adjuvant chemo &/or radiotherapy.⁹

As a small percentage of these tumours recur, patients should be followed up indefinitely.⁹ The mainstay of treatment for localized disease is external-beam radiotherapy (EBRT) with 30 to 36 gray (Gy), usually given in 20 daily fractions of 1.8 Gy. The complete remission rate is in excess of 90 percent for MALT lymphoma, with excellent long-term local control in the majority of patients. The potential complications of EBRT include xerophthalmia, keratitis, cataract formation and retinopathy.¹⁰

The conjunctival defect created during the surgical removal of a large lesion might result in symblepharon¹¹ & hence there is a need to cover the bare sclera by an autograft.

AUTOGRAFTING IN COMBINED NAEVUS

Combined nevi are neoplasms composed of 2 or more distinct melanocytic populations. They comprise any melanocytic nevus, including blue nevus, Spitz nevus, or nevus with deep dermal pigmented cells, combined with another type of nevus. The most common type of combined nevus is that combined with a blue nevus, and it is histologically distinctive.¹²

Combined naevi of conjunctiva are not rare. The blue naevus cells are usually located deeper than most naevocytic naevus cells, may be bluer or grayer than usual naevi, & usually have been pigmented since early in childhood. A correct diagnosis will make surgical excision unnecessary, if an excision is necessary, the surgeon can avoid doing a deep excision involving the sclera. If excision is necessary because of the cosmetic defect, the superficial component could be excised & examined, while the deeper pigment could presumably be eliminated with cryotherapy.¹³

Most studies support observation of cases due to the benign nature of the lesion. In our study we conceded to the patient's wish for the removal of the lesion as it was increasing in size & for cosmetic reasons.

FIBRIN GLUE

Fibrin glue (FG) is a blood derived product that is absorbable, relatively easy to use, stored in a refrigerator. FG includes a fibrinogen component and thrombin component, both prepared by processing plasma. FG forms a smooth seal along the

entire length of the wound and edges and provides better comfort with the least amount of complications, FG uses the mechanism of blood clotting formation by the coagulation cascade resulting in an adhesive glue. There is subsequent proliferation of fibroblasts and formation of granulation tissue within hours of polymerization of fibrin. Clot organization is complete two weeks after application. The resultant fibrin clot degrades physiologically.

Reliseal™ (manufactured by Reliance Life Sciences)¹⁴

The Fibrin glue kit (Reliseal™, manufactured by Reliance Life Sciences Laboratories, India) contains 2 components in separate vials:

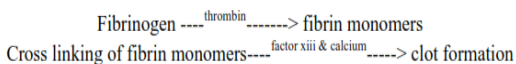
- 1) Freeze dried human fibrinogen
- 2) Freeze dried human thrombin

The kit also contains:

- 1) Aprotinin solution (Bovine) — 3000 & 1500 kallikrein inhibitor units (kiu/ml) in 1ml & 0.5ml units respectively,
- 2) 1 × 5 ml ampoule of sterile water for injection,
- 3) 4×2ml syringes for reconstitution & application,
- 4) 4×21G sterile needles for aspiration of the two components; 2×20G blunt application needles.
- 5) Fibrin glue applicator with two mixing chambers & 1 plunger guide.

Safety & viral inactivation of the product: The product is screened for HIV 1 & 2, Hepatitis B virus, HCV, parvovirus & HAV. Solvent Detergent Technology is used to inactivate lipid coated viruses. Though, there is a remote possibility of an unknown infectious agents to be present in these products.

The fibrin adhesion system initiates the last phase of physiological blood coagulation cascade.



The locally applied mixture quickly sets to form a milky white to translucent mass which continues to gain strength within 2 hrs following application. As wound healing progresses, increased fibrinolytic activity is induced by plasmin & the decomposition of fibrin to fibrin degradation products is initiated. Proteolytic degradation of fibrin is inhibited by aprotinin (plasmin inhibitor). Graft dehiscence is a recognized complication of using tissue glue.¹⁵

MATERIALS AND METHODS

Prospective interventional study done between Jan 2006 to Dec 2014 at Kempegowda institute of

medical sciences & research centre affiliated to RGUHS. Permission & Ethical clearance were obtained. Procedures done according to Organ Transplantation Act & Helsinki guidelines.

Random selection of recurrent pterygia cases were done. After slit lamp evaluation of the extent of the lesion, availability of healthy conjunctiva for grafting at supero temporal quadrant. All the cases were evaluated for tear film stability. Schirmer's test was done to exclude dry eyes. Patients with lid abnormalities lid infections and chronic inflammations of conjunctiva are excluded from the surgery. Of the patients having recurrent pterygia, five had right sided & three were left sided & one case had bilateral pterygium.

History & findings of the cases with combined naevus of conjunctiva & maltoma are given below.

PREOPERATIVE PREPARATION

Demographic data of all the patients recorded. Written consent obtained after they were explained about the procedure of the surgery. Preoperative topical antibiotics instilled for three days, oral antibiotics started twelve hours before surgery. Patients were screened for HIV infections & none tested positive.

OPERATIVE PROCEDURE

All cases were operated under peribulbar anaesthesia. The pterygium was excised in the same manner for all patients, utmost care was taken at the time of dissection of fibrous adhesions to prevent injury of medial rectus insertion. Wings and other irregular extensions of recurrent body were released and excised. The bare area thus created was measured using calipers, a 1 mm wider area was marked on the supero temporal conjunctiva with methylene blue. The graft harvested by separating the epithelial layer from underlying adenoid layer with the help of subconjunctival infiltration of 2% xylocaine. A quadrangular flap of the harvested graft was slid on to recipient area, holding the medial end with McPherson's forceps to avoid curling, rolling or turning of the flap upside down. The graft was then spread over recipient area to avoid wrinkles. Reliseal was reconstituted as per instructions on the packaging & injected on to bed by raising the graft with two way cannula. After five minutes excess glue projecting from edges of the graft was washed away & the donor area was covered with remaining fibrin glue.

The eyes were padded for 12 to 18hrs and the patients were kept under observation in the hospital for 3 days. All cases were prescribed antibiotics (moxifloxacin 0.5%) & loteprednol (0.5%) for three weeks, carboxymethyl cellulose for 3-6 months topically, all patients were advised postoperative U.V. filtering glasses for all outdoor activities. Observations done on the first 3 post operative days, 1st, 2nd & 3rd weeks, 2nd, 3rd and 6th months and few cases were followed upto 8 years.

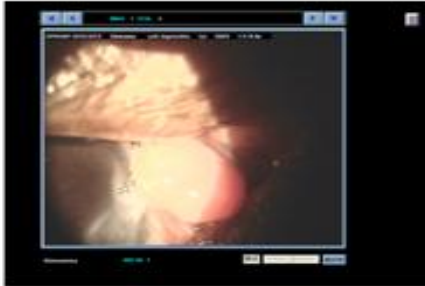
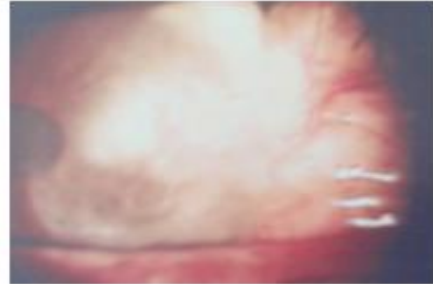


Figure 1: cystic degeneration in a recurrent pterygium & the postoperative photograph of the same patient

OPERATIVE PROCEDURE

Total excision of the mass was done leaving clear margins of 1 to 2mm of healthy conjunctiva (15 mm horizontal & 11 mm vertical), bleeding points were cauterized. The bare area was covered with CA (2 grafts, each of size 5 mm x 5mm) using FG, the graft was obtained from the inferior bulbar and fornical conjunctiva of the same eye. Antibiotic-steroid ointment was applied and the eye was patched. The



2 CASE OF MALTOMA

In Jan 2008, a 55 year old moderately built & nourished female presented with complaints of a painless, gradually progressive swelling in her right eye since 1.5 years, following foreign body sensation and redness of two months duration in the same eye.



Figure 2: conjunctival maltoma

figure 2:

Examination revealed a pink mass, extending from 10 o'clock to 1 o'clock horizontally along the superior limbus and 5mm vertically and a prospective diagnosis of foreign body granuloma was made. Patient refused surgical excision. She was given topical steroids and antibiotics, & was advised follow up visits. The lesion progressed both horizontally and vertically. In Jan 2009 its dimensions were 10 to 4 o'clock horizontally and 10mm vertically. The patient then consented for excision on 16 Jan 2009.

topical treatment was continued for 4 months.

Investigations

Haematology and biochemistry: WNL

Histopathology: Extranodal Marginal zone B cell small Lymphocytic Lymphoma

Immunohistochemistry: Positive for CD20, CD79a, CD23 & Negative for CD30, CD10, CD3, Tdt

Whole body PET scan: WNL

Follow-up: done on 1st and 3rd post operative day, then weekly for six weeks, After 6 weeks patient had no complaints, the whole surgical area was clear and did not show any swelling/infiltration, corneal or conjunctival signs.

Figure 3:

After 4 months- no conjunctival or corneal thinning, no recurrence of the swelling and cosmetically the eye looked just like the normal left eye. In Mar 2010 the patient developed right cortical cataract. She underwent cataract surgery with

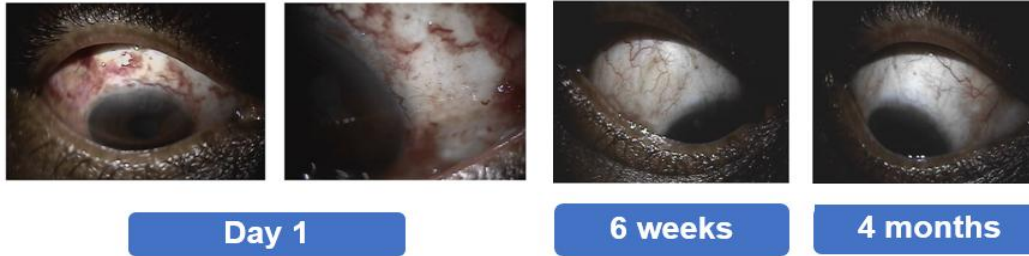


Figure 3 : postoperative images of the same patient following excision of maltoma & autografting

temporal clear corneal incision and postoperative period was uneventful.

3 CASE OF COMBINED NAEVUS

Figure 4: A 16yr old female presented with a black mass in her right eye at the temporal part of the palpebral aperture since birth & was increasing in size over 6 months. On examination the lesion was found extending upto limbus, measuring 6mmx5mm, not vascularized, surface was irregular and raised above the conjunctival surface. The patient wanted surgery for cosmetic reasons.



Figure 4 : conjunctival combined naevus in the right eye pre (right) & postoperative (left) photographs.

Surgical excision of the lesion done & the bare area was covered with CA from same eye using FG, topical antibiotic & steroid drops were prescribed for 3weeks.

Histopathology: combined naevus of the conjunctiva.

Follow-up: done on 1st and 3rd postoperative day, then weekly for six weeks, After 6 weeks the patient had no complaints, the surgical area was clear.

RESULTS AND DISCUSSION

Of the eight eyes with recurrent pterygium who underwent pterygium excision with CA using fibrin glue, 7 had uniform conjunctival surface & did not have irritation, discomfort & recurrence of the lesion. One patient had unevenness of the grafted area due to wrinkling & had foreign body sensation for months, later the patient got adapted & all cases

were followed up for minimum period 2 yrs & maximum period of 5yrs. No recurrences were found in any of the cases studied.

One eye of malt lymphoma, after total excision of the lesion underwent CA with FG, the conjunctival surface became normal by the end of 4 months & no recurrences found after 5yrs of follow up.

One case of combined naevus of limbus underwent local excision then C A using fibrin glue. Conjunctival surface became normal by the end of 2 weeks & no recurrences found after follow up for 5yrs.

Success achieved in 100% of cases as per recurrence, 90% with respect to cosmetic surface reconstruction

Use of FG has made CA easy, with less tissue injury, quick, with least post-operative inflammation and fast recovery. This procedure is adopted in treating conjunctival defects of various conjunctival surgeries. In this study 10 eyes underwent C A to cover ocular surface defects created following excision of various conjunctival lesions. All cases had good reconstruction of the defects and uneventfully regained the normal architecture, none of the cases showed recurrence during a follow up period of 5yrs. Allen BD and Prabhaswat P have also found CA to cover the naked scleral bed as an effective and safe technique, associated with low rates of primary lesion recurrence.^{16,17}

Use of FG made gluing of the graft quick & easy and less damaging to tissues compared to suturing. Patient comfort was good as no sutures were used & no inflammatory reactions found as the graft was an autograft.

Even though several studies have demonstrated that fibrin glue significantly reduces surgery time and improves postoperative patient comfort and cosmesis, there have not been many studies with

respect to the question of recurrences and, the recurrence rate was not evaluated in many studies. Some studies did, however, demonstrate lower rates of recurrence when fibrin glue was used.¹⁸⁻²³

Autografting from superior or inferior quadrants in primary pterygia has no significant difference in recurrence rates, but in recurrent pterygia, autografting from the inferior quadrant resulted in a higher recurrence tendency. Koranyi et al demonstrated a recurrence rate of 5.3% with glue versus 13.5% with sutures and suggested that immediate adherence of the graft and lack of postoperative inflammation may inhibit fibroblast ingrowth and reduce the recurrence.²⁴

In our study graft obtained from the inferior quadrant of the eye did not show any recurrences in malt lymphoma.

The procedure of conjunctival autograft with fibrin glue was painless & free of complications like granuloma formation, inflammations & recurrences, scleral necrosis, irregular scarring, perforations & staphyloma²⁵ use of FG in CA has reduced the surgical time & inflammatory reactions which can occur following suturing the average time consumed during our procedures was 10mins with fibrin glue.

Since the surgical time is lesser, the inflammation & thus recurrences will be lower. The longest series published after using fibrin glue showed a mean recurrence of 4.50% in a series of 111 operated pterygium over a follow-up period of two years.²⁶ This study had a follow up period ranging from 3 to 8 years & has not showed any recurrences. Starc and colleagues in their study with mean follow-up of 2 years detected only three (5.3%) recurrences after autograft transplantation and found a 7.3% secondary recurrence in patients with recurrent pterygium, the most common method of autograft fixation is suturing, with drawbacks of prolonged operating time, postoperative discomfort, suture abscesses, buttonholes, and granuloma formation. Usually requiring a second operation for removal of sutures.²⁷

CONCLUSION

Covering conjunctival defects by CA using FG following thorough dissection and removal of pathologies is a successful procedure to cover the bare area created by any surgical procedures as it is 1)less time consuming, 2) patients comfort is good

3)cosmetic outcome is good 4) achieved normal architecture 5)no recurrences were found.

Currently, no reports are available to compare the surgical results of CA in cases of combined naevus & MALT lymphoma. This study showed that the surgical defects created by excision of such conjunctival pathologies can also be covered with CA. The important requirement is to excise the diseased tissue completely to get healthy & disease free margins, disease free margins were obtained here by marking the surgical incision using methylene blue marker pen 1-2mm beyond the visible pathology.

The use of conjunctival autograft using fibrin glue is a successful procedure in reconstruction of surgical ocular surface defects as seen in cases of recurrent pterygia, case of conjunctival MALToma & also in a case of combined naevus.

This study shows that with CA using FG has low postoperative discomfort, no recurrences & also good cosmesis. This may be attributed to biocompatible nature of fibrin glue which avoids complications of sutures and diminishes the sensation of a foreign body in the eye following surgery.

The problem of high cost of fibrin glue can be overcome by using the glue for operating on multiple pooled patients at a time, as only a small amount of glue is required per case. FG also avoids the need for a separate follow-up for suture removal.

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