

**Preserving conjunctiva, the 'real estate' of glaucoma surgeons**

**Abstract**

Glaucoma management is as challenging as diagnosing it. Achieving sustained intraocular pressure that will retard the progression of the disease is the principal objective of its management. Many a times, this requires a combination of antiglaucoma medications, Lasers and surgery. No doubt, medical therapy is usually the mainstay of glaucoma management but in some cases, it fails to adequately control the intraocular pressure. The very effective surgical interventions for glaucoma depend on the health of the conjunctiva to achieve their success. So, meticulous evaluation of the conjunctiva is one of the indispensable preoperative considerations before deciding on any conjunctiva-dependent surgery. In addition, in managing any patient with ocular problem who also has glaucoma, it is imperative that the possibility of future surgery involving the conjunctiva must be considered. Therefore, the conjunctiva of all glaucoma patients must be handled with care.

**Keywords: Glaucoma surgeon, Conjunctiva, Real estate, surgical outcome**

**Introduction**

Glaucoma as a condition of multiple aetiology is managed with medications, lasers and surgery<sup>1</sup>. Over the spectrum of management, one modality or a combination of the various

modalities can be applied in order to achieve the target intraocular pressure with a view to slowing the progression of the disease.

Surgical intervention is traditionally indicated when maximal tolerable medical therapy fails to adequately control the intraocular pressure with attendant disease progression.<sup>2</sup> However, surgery can be used as the first line treatment especially in advanced cases. The surgeries for glaucoma can be broadly classified as conjunctiva dependent and independent.<sup>2,3</sup> Conjunctiva dependent surgeries include Trabeculectomy, Tube shunts, and non-penetrating glaucoma surgery. Conjunctiva -dependent surgeries majorly known as filtration surgery, are the most effective means of reducing intraocular pressure.<sup>2</sup> The conjunctiva-independent surgery include trabectome, iStent, Gonioscopy-assisted transluminal trabeculotomy(GATT), Kahook dual blade goniotomy, hydrus microstent ab-interno canaloplasty<sup>3, 4</sup>

Conjunctiva based surgeries need healthy conjunctiva for optimum success. It is imperative for glaucoma surgeons to meticulously evaluate the health of the conjunctiva before embarking on any conjunctiva-based surgery. The conjunctiva can be considered the 'real estate' for the glaucoma surgeon which deserves all attention and care. This is because glaucoma filtration surgeries are conjunctiva dependent. Among other factors, properly performed trabeculotomy had failed because of unhealthy conjunctiva either due to fibrosis from previous ocular surgery or prolonged exposure to topical antiglaucoma medications especially prostaglandin analogues.<sup>5</sup>

This article is intended to review how the conjunctiva can be optimized for the Glaucoma surgeons in order to achieve successful surgical outcomes when surgery is indicated.

## Gross anatomy and histology of conjunctiva

The conjunctiva is thin translucent mucous membrane that lines the anterior and posterior (inner) surfaces of the eye the eyeball (bulbar conjunctiva) and eyelids (palpebral conjunctiva) respectively.<sup>6-8</sup> There is the third part which line the fornices and is called the fornicial conjunctiva. It is derived from the term "*conjoin*", meaning *to join*" From the posterior surface of the lid which it covers, it reflects to cover the sclera anteriorly and bends in the same direction with the cornea epithelium and with the lid skin at the margins.<sup>6</sup> It produces mucin and tears which provides lubrication and protection to the eyes.<sup>7</sup> The conjunctiva is rich in blood and lymphatic vessels.

The bulbar (ocular) conjunctiva is sub divided into the limbal and the scleral parts, at the sclera, it is bound by the tenon's capsule. The fornicial conjunctiva divided into the inferior, lateral medial and superior region while the palpebral (tarsal) conjunctiva. The conjunctival fornices is the junction between the bulbar and palpebral conjunctiva.<sup>7</sup>

The conjunctival epithelium is about 3–5 cell layers thick. The cells are predominantly non-keratinized stratified squamous epithelial cells which contains mucus secreting goblet cells, Langerhan's cell which are immune cells and occasionally melanocytes.<sup>7,8</sup> The goblet cells secretions contribute to the tear film which serve lubricating and protective functions. Also within the epithelial layers is the conjunctiva-associated lymphoid tissues (CALT) made up of lymphocytes. CALT is critical in the immunology of the ocular surface. It has been reported that the lymphatic system of the conjunctiva is critical to the long-term success of glaucoma filtration surgeries.<sup>2</sup> Underlying the epithelial cells is the highly vascularized loose connective tissue, the stroma (or substantia propria).<sup>8</sup> The vascularized stroma play an important role in

conjunctival wound healing. The conjunctival surgical anatomy of interest in glaucoma surgery is the loose and flexible consistency of the unscarred bulbar conjunctiva.<sup>2,9</sup>

### **Conjunctiva injury and healing**

Conjunctival injury and healing is a complex interplay between growth factors, cytokines, enzymes and cross-talk between different groups or types of cells.<sup>10-11</sup> Injury may follow acute or chronic insult to the conjunctiva. The former (acute) includes accidental or intentional trauma from mechanical injury, surgical wound (cataract surgery, conjunctival graft in pterygium and other surgical procedures), and chemical burns. The later include chronic inflammation and ocular surface deficiency which follow prolonged exposure to preservatives from topical medications such as benzalkonium chloride in many eye drops, including anti-glaucoma medications. Conjunctival wound healing follows the classical four stages of wound healing similar to what happens in the skin, which are; haemostasis, inflammation, proliferation. Healing involves plasma protein (fibrinogen, plasminogen and fibronectin) and blood cells (platelet, polymorphonuclear neutrophils and red blood cells) leakages from compromised vasculature.<sup>12</sup> This triggers the clotting reaction cascade where fibrin clot is formed by conversion of fibrinogen to fibrin, leading to coagulation.<sup>10</sup> These two events (release of protein and clot formation) results in migration and attraction of neutrophil, macrophages and lymphocytes to the site of injury during the initial inflammatory phase. Remodeling which part of the last stages of wound healing regulates the amount of scar tissue at the end of the healing process.<sup>10-12</sup>

### **How to preserve conjunctiva for optimum glaucoma surgery**

It was earlier mentioned that the conjunctiva is considered as the 'real estate' of the glaucoma surgeon because the success of most glaucoma filtration procedures (such as trabeculectomy, deep sclerectomy, Ex-PRESS implant surgery, InnFocusMicroShunts®, XEN glaucoma implants etc.) is dependent on the structural integrity of the conjunctiva.<sup>13-14</sup> This justifies the advocacy for preservation of the conjunctiva by glaucoma specialists and indeed any ophthalmologist involved in glaucoma care.

Certain conjunctival sparing techniques have been recommended for conjunctiva preservation, especially in people likely to benefit from a conjunctiva dependent glaucoma surgery in the future. For instance, excessive dissection of the conjunctiva in conventional extracapsular cataract extraction and small incision cataract surgery, predisposes to conjunctival scarring and fibrosis. On the other hand, procedures that access the anterior chamber through a limbal or clear corneal section such a phacoemulsification have been advocated.<sup>9</sup>

The conjunctiva also serves as a donor site for auto grafts and flaps. Auto grafts are indicated as adjunctive procedures following pterygium excision in order to prevent recurrence. Also, oculoplastic procedures such as repair of a lid defect may need grafts which may be sourced from the conjunctiva. It is being advocated that such grafts should be harvested from other parts of the bulbar conjunctiva in order to preserve the superior portion which is the choice filtration site. Previous studies by Syam *et al*<sup>15</sup>, Kim *et al*<sup>16</sup>, Koc *et al*<sup>17</sup>, and Shrestha *et al*<sup>18</sup> successfully demonstrated that superiorly sourced conjunctival grafts had no significant advantage over grafts obtained from the inferior bulbar conjunctiva. This makes inferior conjunctival autografting for pterygium surgery a viable alternative for preserving the glaucoma filtration site especially in patients likely to benefit from a future filtration surgery.

Alternatively, since the grafts are preferably harvested from the supero-temporal bulbar conjunctiva<sup>19</sup> the glaucoma surgeon may use a more medial approach during filtration surgeries. Also, since careful dissection of the conjunctiva from the underlying tenon's capsule is needed for optimum success of the graft in pterygium surgery,<sup>19</sup> it will also minimize scarring at the donor site which can also contribute to the preservation of the conjunctiva.

The effects of implicated preservatives have also been noted to be dose related, and it has been advocated that reducing the frequency of exposure may equally help in preserving the conjunctiva. This has birthed the use of fixed dose combination also limiting the use of timolol to once daily have been recommended.<sup>20-22</sup>

### **Ocular surface diseases (OSD)**

There is a complex relationship between glaucoma, its management and ocular surface diseases. This is akin to an old unanswered question – 'the egg and the hen, which of them came first?' Glaucoma is more prevalent among older people who have already developed some OSD from goblet cell dysfunction and unstable tear film. Also, most topical medications which include many commercially available anti-glaucoma medications. Long term use of these topical antiglaucoma medication can exacerbate existing OSD due to the preservatives they contain which can stimulate pro-inflammatory cytokines which predispose to apoptosis, oxidative stress and interact directly with the lipid component of the tear film.<sup>23,24</sup> Chronic conjunctival inflammation from these preservatives have been linked with compromise and failure of filtration surgery.<sup>23,24</sup> Also, intraoperative exposure to mitomycin-c, 5-fluorouracil, presence of blebs with thin walls (which are deficient in the required goblet cells density and with the virgin conjunctiva) or dellen formation all contribute to exacerbation of pre-existing or

development of new OSD. The use of preservative free topical medication such as preoperative anti-glaucoma medications, tears substitute pre or post-operative steroids can induce reversal of some of these conditions. Also immune modulators like cyclosporine have been shown to be helpful as adjunctive treatments in patient with OSD.<sup>25</sup> In some cases, the ocular surface may still not be ideal for optimum surgery, the glaucoma surgeon may be constrained to either operate like that or use an alternative therapeutic strategy such a minimally invasive glaucoma surgeries (MIGS), laser trabeculoplasty with insertion of bimatoprost implants 10µg (Durystra Allergan).<sup>26</sup> Also conjunctiva can be mobilized for flaps under which a tube drainage shunt is inserted.

### **Challenges of preserving the conjunctiva**

The challenges related to surgeries and preservation of the conjunctiva depends on the skills of the surgeon and choice of surgical site in the different procedures as listed earlier.<sup>9, 15-19</sup>

Recommended alternative delivery systems are currently not readily available globally due to skill gaps. Even when the skill is available it may be inaccessible due to cost and lack of insurance coverage in lower income economies.

Access to preservative free medications is another possible challenge as most manufacturers are in the developed economies and by the time they get to certain markets, their potencies may no longer be guaranteed, in addition to the risk of contamination.<sup>20</sup>

The use of different medications (anti glaucoma medications, tears substitutes, steroids cyclosporine, and doxycycline in some cases) may also be very burdensome to the patient due to access, availability and affordability.<sup>27</sup> Also, older glaucoma patients are likely to have other

comorbid conditions which require treatment. This amounts to polypharmacy with attendant issues of compliance for different reasons, side effects and overall health of the patients.

Topical steroid is one of the anti-inflammatory pre-medications recommended to improve the ocular surface prior to filtration surgery. Dexamethasone which is the most potent steroid is known to be associated with elevation of intraocular pressure (IOP) and infection.<sup>27</sup> Pre-surgery IOP elevation may be counterproductive while occult preoperative infections linked to steroids use can predispose to endophthalmitis which is one of the most dreaded nightmares of any ophthalmic surgeon.

So far, a lot of strategies have been suggested for the preservation of the conjunctiva and other ocular surfaces. There is a knowledge gap with respect to reliable evidence for credible peer reviewed sources and guidelines. So, glaucoma surgeons still rely on expert opinion and experience which is the lowest level of clinical evidence. There is an urgent need for more reliable evidence in order to cover this knowledge gap for improving glaucoma care.

## **Conclusion**

The glaucoma surgeon must consider the risk benefit of prescribed medications for glaucoma management not just for the quality of life of the patients but for the health of the conjunctiva for possible surgery in the future. Previous ocular surgeries involving the conjunctiva predispose to failure of conjunctiva-dependent glaucoma surgery. Having a loose and unscarred conjunctiva should be the focus of the Glaucoma surgeon. Therefore, the surgeon should try to optimize the health status of the conjunctiva before carrying out any such conjunctiva-based

surgery for glaucoma. The conjunctiva remains the most important surgical resource for the Glaucoma surgeon.

### References:

1. Samples RJ, Singh K, Lin SC, Francis BA, Hodapp E, Jampel HD et al. Laser trabeculoplasty for open-angle glaucoma: a report by the American academy of ophthalmology, *Ophthalmology* 2011; 118: 2296-2302.
2. Yu D, Morgan WH, Sun X, Su Er, Cringle SJ. The critical role of the conjunctiva in glaucoma filtration surgery. *Prog Ret Eye Res.*2000; 28: 303-328.
3. Francis BA, Singh K, Lin SC, Hodapp E, Jampel HD, Samples JR, et al. Novel glaucoma procedures: A report by the American Academy of Ophthalmology. *Ophthalmology.* 2011;118:1466–80.
- 4.[https://eyewiki.aao.org/Microinvasive\\_Glaucoma\\_Surgery\\_\(MIGS\)#cite\\_note-samples4-4](https://eyewiki.aao.org/Microinvasive_Glaucoma_Surgery_(MIGS)#cite_note-samples4-4). Accessed May 31 2023
- 5.cott IU, Greenfield DS, Schiffman J, Nicoleta MT, Rueda JC, Tsai JC et al. Outcomes of primary trabeculectomy with the use of adjunctive mitomycin. *Arch Ophthalmol* 1998; 116: 286-291.
6. Majumder PD. Anatomy of the conjunctiva. Available online from <https://www.eophtha.com/posts/anatomy-of-conjunctiva>. Accessed May 5, 2023.
7. Shumway CL, Motlagh M, Wade M. Anatomy, Head and Neck, Eye Conjunctiva. [Updated 2022 Aug 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK519502/>. Accessed May 2023

8. Awh C, Wilson MW, Grasmeyer J. Basic histology of the eye and accessory structures. Available online from [https://eyewiki.aao.org/Basic\\_Histology\\_of\\_the\\_Eye\\_and\\_Accessory\\_Structures](https://eyewiki.aao.org/Basic_Histology_of_the_Eye_and_Accessory_Structures). Accessed January 5, 2023.
9. Piltz-Seymour JR, Valley H. Glaucoma surgery: when: the conjunctiva isn't ideal. Available from <https://www.reviewofophthalmology.com/article/glaucoma-surgery-when-the-conjunctiva-isnt-ideal>. Accessed October 16, 2022.
10. Khaw PT, Bouremel Y, Brocehini S, Henein C. The control of conjunctival fibrosis as a paradigm for the prevention of ocular fibrosis related to blindness. "Fibrosis has many friends". Eye 2020; 34: 2163–2174.
11. Van Bergen T, Van de Velde S, Vandewalle E, Moons L, Stalmans I. Improving patient outcomes following glaucoma surgery: state of the art and future perspectives. Clin Ophthalmol 2014; 2:857-867.
12. Stages of wound healing. Available online from <https://www.uptodate.com/contents/image/>. Accessed January 22, 2023.
13. King AJ, Shah A, Nikita E, Hu K, Mulvaney CA, Stead R et al. Subconjunctival draining minimally invasive glaucoma devices for medically uncontrolled glaucoma. Cochrane Database Syst Rev. 2018; (12). doi: 10.1002/14651858.CD012742.pub2.
14. Shaarawy T. Glaucoma surgery: taking the sub-conjunctival route. Middle East Afr J Ophthalmol. 2015; 22:53–58.
15. Syam PP, Eleftheriadis H, Liu CS. Inferior conjunctival auto graft for primary pterygia. Ophthalmology. 2003; 110:806–810.

16. Kim S, Yang Y, Kim J. Primary pterygium surgery using the inferior conjunctival transposition flap. *Ophthalmic Surg Lasers*. 1998;29: 608–611.
17. Koc F, Demirbay P, Teke MY, et al. Primary and recurrent pterygium conjunctival autografting. *T Oft Gaz*. 2002; 32:583–588.
18. Shrestha A, Shrestha A, Bhandari S, Maharjan N, Khadka D, et al. Inferior conjunctival autografting for pterygium surgery: an alternative way of preserving the glaucoma filtration site in far western Nepal. *Clin Ophthalmol*. 2012; 6: 315–319.
19. Aminlari A, Singh R, Liang D. Management of Pterygium. Available online from <https://www.aao.org/eyenet/article/management-of-ptyerygium-2>. Accessed January 22, 2023.
20. Bagnis A, Papadia M, Scotto R, Traverso C E. Antiglaucoma drugs: The role of preservative-free formulations. *Saudi J Ophthalmol*. 2011; 25:389–394.
21. Baudouin C. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. *Acta Ophthalmol* 2008; 86: 716– 726.
22. Baudouin C, Labbe A, Liang H, Pauly A & Brignole-Baudouin F. Preservatives in eye drops: the good, the bad and the ugly. *Prog Ret Eye Res*. 2010;29: 312–334.
23. Benitez-Del-Castillo J, Cantu-Dibildox J, Sanz-Gonzalez SM, Zanon-Moreno V, Pinazo-Duran MD. Cytokine expression in tears of patients with glaucoma or dry eye disease: a prospective, observational cohort study. *Eur J Ophthalmol*. 2019; 29:437-443.
24. Baudouin C, Labbe A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res*. 2010; 29:312-334.

25. Agnifili L, Fasanella V, Mastropasqua R, Frezzotti P, Curcio C, Brescia L et al. In vivo goblet cell density as a potential indicator of glaucoma filtration surgery outcome. Invest Ophthalmol Vis Sci. 2016; 57:2928-2935.
26. Voicu LA. Management of ocular surface disease before and after glaucoma surgery. Available online from <https://glaucomatoday.com/articles/2021-may-june/management-of-ocular-surface-disease-before-and-after-glaucoma-surgery>. Accessed November 23, 2022.
27. Agnifili L, Sacchi M, Figus M, Posarelli C, Lizzio RAU, Nucci P et al. Preparing the ocular surface for glaucoma filtration surgery: an unmet clinical need. Acta Ophthalmologica 2022; 100: 740–51.