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REVIEW ARTICLE

Collagen Cross-linking and Bleb Leaks: Sealing the Leak

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Abstract

This brief review explores the use of Conjunctival crosslinking as a viable method for the management of leaking trabeculectomy blebs. CXL can be used in conjunction with bandage contact lenses for the effective treatment of late onset bleb leaks prior to considering surgical intervention.

Bleb leaks are a known complication post various glaucoma filtering procedures with a reported incidence ranging around 11–15% in 5 years.[1,2] Bleb leaks can have potentially vision threatening complications such as hypotony and blebitis that might even progress to bleb related endophthalmitis.[3] Hence, a prompt diagnosis and timely management is crucial.

Depending on the time of presentation bleb leaks can be characteristically classified as early onset bleb leaks (within 2 weeks of surgery) and late onset bleb leaks.[4] The etiology and the management differ to cater to specific causes of the leak in early or late postoperative period. The early bleb leaks are generally secondary to inadequate conjunctival closure, buttonholing, or conjunctival retraction and hence, the management would involve restoring the conjunctival integrity.[5] On the other hand, late onset bleb leaks tend to present months to years after the filtering surgery. These leaks are associated with thin, ischemic and cystic blebs.[3] High flow leaks have frank Seidel's positive test, while low flow leaks present with pinpoint transconjunctival ooze (sweating bleb).[6]

Late onset leaks result due to subconjunctival fibrosis around the bleb that restricts the aqueous outflow causing the pressure within this limited area to increase and thereby stretching the overlying conjunctiva and causing microdamage to the overlying conjunctival epithelium. On histopathology, characteristic hypocellularity and basement membrane breakdown is seen.[7] Use of anti-fibrotic agents like Mitomycin C (MMC) and 5-Fluoro-uracil has shown an increase in the incidence of cystic blebs and more chances of bleb leaks.[8,9] Such late leaks can be managed using fibrin glue, autologous serum, or cyanoacrylate glue at the site of leak with variable success, especially in scenarios where the leaks are more diffuse. Surgical management involves bleb excision with conjunctival advancement or amniotic membrane transplantation, again a challenging scenario in the setting of adjoining scarred and fragile conjunctiva.

To overcome these issues, a less invasive approach treating the affected area with collagen cross-linking (CXL) has come into vogue. CXL aims at strengthening the already existing tissue by creating covalent bonds by exposing the affected conjunctival tissue soaked in riboflavin to UVA light. The procedure for corneal CXL has shown definitive success in various corneal ectatic disorders[10] and taking a cue from the same CXL has been tried in bleb leaks as well.

CXL results in formation of covalent bonds within the collagen lamellae of the treated tissue. The cystic blebs, especially the ones which are treated with prior high dose MMC, are deficient in collagen. However, most of these blebs have fibrovascular proliferation at their edges. CXL not only targets the residual collagen lamellae but also acts on the fibroblasts which are stimulated to produce more extracellular matrix, resulting in strengthen the bleb.[11,12]

Although CXL is a promising procedure, it is still in early stages to establish itself as a valid treatment option for bleb leaks. We looked at the available published literature so far.

Efficacy of CXL procedure was also studied in the cattle conjunctiva by Chan *et al*., where a decreased conjunctival permeability and increased resistance to rupture in the CXL treated conjunctiva was noted.[13] The histopathological effects of the CXL treatment over rat conjunctiva were studied by Zhu and colleagues. They observed inhibition of lymphangiogeneis and angiogenesis in the area of conjunctival vascularisation for initial 7 days followed by increase in the cytokine levels that promoted angiogenesis and lymphangiogenesis thus aiding healing.[14]

Jordi *et al*. have also shown that remaining fibroblasts and the growth-arrested cells around the margin of the ischemic blebs stimulatea a fibrovascular repair post-CXL.[15]

Cai *et al*. in their prospective case series treated 12 eyes with late onset bleb leaks with CXL using 0.1% riboflavin that was soaked on to the conjunctival surface for 30 min and subjected to UVA irradiation at a dose of 3 mW/cm^2 for 30 min. CXL showed resolution of leakage in 11 out of 12 eyes over a median time interval of 3 weeks. The bleb thickness was also significantly increased at 3 months and the blebs performed well over a follow-up period of 12 months.[9]

In another prospective case series of five patients with cystic bleb leaks, Choy *et al*. showed cessation of leak in two out of five eyes in 1 week, one eye over 2 weeks, and in the rest two complicated cases over 4 weeks. The bleb continued to function well over 33 weeks. The CXL treatment details included, soaking period of 30 min using 0.1% Riboflavin and irradiation time of 30 min at a dosage of 3 mW/cm^2.[16]

Wang and colleagues in their retrospective case series treated seven eyes with late onset bleb leaks with CXL and showed complete resolution in five out of seven cases (71%). The eyes showed non-resolution of leaks despite prior conservative medical management trial given for 1 month before intervention. CXL procedure had a soaking time of 30 min with 0.1% riboflavin, followed by irradiation with UVA light at a dose of 2 mW/cm^2 for 30 min.[11]

Aktas *et al.* reported a single case of bleb leakage following a trabeculectomy that was done 10 years prior to the observed leak. Initially, injection of autologous blood was tried, but with recurrence of leakage the bleb was treated with CXL using hypertonic riboflavin and irradiation for 10 mins along with application of contact lens for 3 days. There was persistent leakage at 1 week, which prompted another sitting of CXL treatment after 1 week. Following this, the leakage ceased and the bleb continued to function well over a period of 12 months. The exact duration and dosage of UVA irradiation were not specified.[17]

Bubalo *et al*. compared CXL with riboflavin versus conjunctival sliding and conjunctival autologous graft for hyper-filtrating ischemic blebs and concluded that CXL did not have an effect on the revitalization of the bleb.[18]

Review of existing literature suggests that CXL is a viable and promising non-invasive management option for treating late onset bleb leaks. However, paucity of enough prospective studies and a variable dosage profile for the CXL treatment limits its widespread usage. CXL applied in conjunction with bandage contact lenses may be used as a competent second line of management for cases that have not responded to conservative line of management before resorting to a more invasive surgical treatment.

References

1. Gedde SJ, Singh K, Schiffman JC, Feuer WJ, Tube Versus Trabeculectomy Study Group. The Tube Versus Trabeculectomy Study: Interpretation of results and application to clinical practice. Curr Opin Ophthalmol 2012;23:118-26.
2. Bindlish R, Condon GP, Schlosser JD, D'Antonio J, Lauer KB, Lehrer R. Efficacy and safety of mitomycin-C in primary trabeculectomy: Five-year follow-up. Ophthalmology 2002;109:1336-41; discussion 1341-2.
3. Feldman RM, Altaher G. Management of late-onset bleb leaks. Curr Opin Ophthalmol 2004;15:151-4.
4. Azuara-Blanco A, Katz LJ. Dysfunctional filtering blebs. Surv Ophthalmol 1998;43:93-126.
5. Alwitry A, Rotchford A, Patel V, Abedin A, Moodie J, King AJ. Early bleb leak after trabeculectomy and prognosis for bleb failure. Eye (Lond) 2009;23:858-63.
6. Senthil S, Basia A, Rao HL, Choudhari N, Dikshit S, Mandal AK, *et al*. Outcomes of bleb repair for delayed bleb leaks and sweating blebs. J Glaucoma 2018;27:33-40.
7. Shields MB, Scroggs MW, Sloop CM, Simmons RB. Clinical and histopathologic observations concerning hypotony after trabeculectomy with adjunctive mitomycin C. Am J Ophthalmol 1993;116:673-83.
8. Belyea DA, Dan JA, Stamper RL, Lieberman MF, Spencer WH. Late onset of sequential multifocal bleb leaks after glaucoma filtration surgery with 5-fluorouracil and mitomycin C. Am J Ophthalmol 1997;124:40-5.
9. Cai Y, Choy BN, Zhu MM, Li BB, Chan JC, Ho WL, *et al*. Prospective study on a novel treatment for leaking cystic bleb: Efficacy and safety of collagen crosslinking. Clin Exp Ophthalmol 2019;47:749-56.
10. Randleman JB, Khandelwal SS, Hafezi F. Corneal cross-linking. Surv Ophthalmol 2015;60:509-23.
11. Wang Q, Harasymowycz P. Collagen cross-linking for late-onset bleb leakage: 1-Year results. J Glaucoma 2016;25:e273-6.
12. Elner VM, Newman-Casey PA, Patil AJ, Flint A, Biswas J, Moroi SE, *et al*. Aberrant wound-healing response in mitomycin C-treated leaking blebs: a histopathologic study. Arch Ophthalmol 2009;127:1036-42.
13. Chan HM, Choy BN, Lai JS. Effects of riboflavin and ultraviolet illumination on the biomechanical properties of conjunctiva. Ophthalmic Res 2018;60:87-93.
14. Zhu Y, Li L, Reinach PS, Li Y, Ge C, Qu J, *et al*. Corneal collagen cross-linking with riboflavin and UVA regulates hemangiogenesis and lymphangiogenesis in rats. Invest Ophthalmol Vis Sci 2018;59:3702-12.
15. Jordi LA, Gustavo T, Aina MU, Nevena R, Pau R. Conjunctival leaking bleb after cross-linking using riboflavin and UVA: A histopathological study. J Clin Res Ophthalmol 2017;4:22-4.
16. Choy BN, Zhu MM, Shum JW, Ho WL, Chan JC, Ng AL, *et al*. Collagen crosslinking in the management of leaking cystic blebs: A prospective study. Graefes Arch Clin Exp Ophthalmol 2016;254:529-33.

17. Aktas Z, Aribas YK, Bilgihan K, Tefon AB. Collagen crosslinking-assisted treatment of a bleb leak: Enhancement of vascularization around the Bleb. J Curr Glaucoma Pract 2021;15:36-9.
18. Bubalo NR, Arenas JL, Romero PP, Udina AM, Mazzon SG, Aljaro PD. Management of the hyper-filtrating ischaemic bleb: Crosslinking with riboflavin and UV radiation versus a conjunctival sliding flap and conjunctival autologous graft. Arch Soc Esp Oftalmol (Engl Ed) 2020;95:64-70.

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