Collagen Cross-Linking for Late-onset Bleb Leakage: 1-Year Results

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Purpose: To assess the efficacy of collagen cross-linking in the treatment of late-onset bleb leakage.

Methods: A retrospective, interventional case-series. Cross-linking was performed for late-onset bleb leakage after failure of standard medical therapy. Primary outcome is measured by complete resolution of bleb leakage. Secondary outcomes including intraocular pressure and corrected distance visual acuity (CDVA) were documented over 1 year and were analyzed using repeated measure ANOVA.

Results: Seven patients underwent cross-linking for bleb leakage between 2012 and 2013. Five (71%) had complete resolution of bleb leakage. Intraocular pressure improved from 3.9 ± 1.0 to 7.4 ± 1.1 mm Hg at 1 to 2 months (P = 0.0003) and remained at 9.6 ± 3.0 mm Hg at final visit (P = 0.06). The corresponding CDVA also improved from 0.6 ± 0.2 to 0.38 ± 0.37 logMAR (P = 0.0069) at 1 to 2 months before stabilizing at 0.38 ± 0.44 (P = 0.0021) at 1 year. Two cases (29%) had persistent bleb leakage after treatment. Four patients (57%) had resolved hypotony (≥ 6 mm Hg) at final visit. No adverse event was reported.

Conclusions: Collagen cross-linking is a noninvasive treatment offering reasonable success rate for filtering bleb leakage, and may spare patients invasive surgical bleb revisions.

Key Words: delayed onset bleb leakage, collagen cross-linking, nonincisional procedure (J Glaucoma 2015;00:000–000)

Late-onset filtering bleb leakage (> 3 mo) is common after trabeculectomy. Potential complications such as hypotony, blebitis, and endophthalmitis can be devastating. Its incidence increases with the use of antibiotic agents.1 Traditional approach to bleb leakage includes conservative medical treatment, nonincisional2 and incisional procedures.4

Collagen cross-linking (CXL) with riboflavin and ultraviolet A induces covalent bonding between collagen fibers and is widely used for corneal ectatic disorders.5 However, its effects on conjunctival tissues, we adopted our center’s current CXL treatment protocol for corneal ectatic disorders and applied it over the leaking blebs. Before CXL, we performed a 30-minute riboflavin (riboflavin-5-phosphate 0.1%/20%; Haber’s Compounding Pharmacy, Toronto, ON, Canada) loading with regular application (q 2 min) on the leaking bleb. We then exposed the treatment area to ultraviolet A beams (UV-X, wavelength: 365 ± 10 nm, irradiance: 2 mW/cm², IROC AG, Zurich, Switzerland) for another 30 minutes during which regular riboflavin application continued. A shield was held by a nurse to prevent CXL of the cornea. If a bleb was not judged to be too thin clinically, the surface was deep epithelialized with a Weck-Cel and alcohol. A routine regimen of moxifloxacin (Vigamox; Alcon Canada Inc., Mississauga, ON, Canada) qid for 1 week and a tapering dose of prednisolone acetate 1% (Sandoz Canada Inc., Boucherville, QC, Canada) over 12 days (tid, bid, daily q 4 d) was given to every patient.

Procedure

For lack of data on CXL parameters on conjunctival tissues, we adopted our center’s current CXL treatment protocol for corneal ectatic disorders and applied it over the leaking blebs. Before CXL, we performed a 30-minute riboflavin (riboflavin-5-phosphate 0.1%/20%; Haber’s Compounding Pharmacy, Toronto, ON, Canada) loading with regular application (q 2 min) on the leaking bleb. We then exposed the treatment area to ultraviolet A beams (UV-X, wavelength: 365 ± 10 nm, irradiance: 2 mW/cm², IROC AG, Zurich, Switzerland) for another 30 minutes during which regular riboflavin application continued. A shield was held by a nurse to prevent CXL of the cornea. If a bleb was not judged to be too thin clinically, the surface was deep epithelialized with a Weck-Cel and alcohol. A routine regimen of moxifloxacin (Vigamox; Alcon Canada Inc., Mississauga, ON, Canada) qid for 1 week and a tapering dose of prednisolone acetate 1% (Sandoz Canada Inc., Boucherville, QC, Canada) over 12 days (tid, bid, daily q 4 d) was given to every patient.

Statistical Analysis

Data were presented as mean ± SE of the mean (minimum to maximum). Repeated measure ANOVA using a mixed linear model (SAS 9.3; SAS Institute Inc., Cary, NC) was performed to compare CDVA and IOP at the 3 postoperative times to their pre-CXL values. A Bonferroni correction was done for multiple comparisons. A P-value of < 0.05 was considered significant.
RESULTS

We have identified 7 eyes from 7 patients (F: 4; M: 3) with an average age of 71.1 ± 4.3 (60 to 90) years. Four patients were whites, 2 were African Canadians, and 1 was Hispanic. There were 3 right eyes and 4 left eyes. They were consecutive bleb leakage cases consenting to CXL treatment. All received a standard intraoperative dose of 0.5 mg/mL of mitomycin-C (MMC) for 1 minute during initial trabeculectomy. Before bleb leakage, the average IOP was 10 ± 1.3 (8 to 16) mm Hg. Baseline CDVA was 0.3 ± 0.1 (0.1 to 1) logMAR.

The average onset of bleb leakage was 86.9 ± 16.4 (30 to 144) months posttrabeculectomy. The leaking blebs were commonly ischemic but varied in size. Loculations were present in 4. Because of the limiting nature of a retrospective study, the specific locations of bleb leakages were only available in 5 patients (Table 1). Bleb leakages were evaluated using the Indiana Bleb Appearance Grading Scale.6 Two had S1 leakage, whereas the rest had S2. Glaucoma medications were stopped. Standard conservative medical treatments included moxifloxacin (Vigamox; Alcon Canada Inc.) qid, atropine 1% (Isopto Atropine; Alcon Canada Inc.) bid, and aggressive surface lubrication. Three patients also failed bleb needling without MMC. As leakage persisted despite the above-mentioned therapy, CXL was performed at 12 ± 6.8 (1 to 47) months after its initial diagnosis. The average pre-CXL IOP was 3.9 ± 1.0 (1 to 7) mm Hg and the CDVA was 0.6 ± 0.2 (0.2 to 1.3). During CXL, only patient no. 2 had thick enough tissue to undergo deepithelialization.

Patients were followed for 15.1 ± 2.0 (9 to 24) months following CXL. At first postoperative visits, 5 (71%) had resolved bleb leakage, whereas 2 patients (no. 3 and 7) (29%) demonstrated S1 leakage. Patient no. 3 was subsequently treated with argon laser with success, whereas patient no. 7 declined further intervention. Except for short-lasting ocular foreign body sensation reported by 4 patients (57%) on their first post-CXL visit, no other adverse effect was reported. Hypotony improved in all patients at first visit. The average IOP was 7.4 ± 1.1 (6 to 10), 7.8 ± 2.4 (4 to 19), and 9.6 ± 3.0 (3 to 24) mm Hg at post-CXL 1 to 2 months (P = 0.0003), 3 to 6 months (P = 0.02), and final visit (P = 0.06), respectively. Four patients (57%) maintained their IOP > 6 mm Hg on the last visit. The average CDVA improved to 0.38 ± 0.37 (P = 0.0069), 0.20 ± 0.19 (P = 0.0012), and 0.38 ± 0.44 (P = 0.0021) at the 3 time points. All patients had improvement in their CDVA post-CXL, but patient no. 5 regressed due to hypotony maculopathy despite a negative Seidel test (Table 1).

DISCUSSION

With reported incidence from 3.3% to 12.9%,7–11 late-onset bleb leakage is often associated with thin, ischemic blebs.12 The use of antifibrotic agents such as MMC and 5-fluorouracil further increases the risk.9–11 In our study, all patients received intraoperative MMC, supporting this association.

While some leakages can resolve with conservative topical treatments, others may require nonincisional and/or incisional procedures.12 In our usual practice, further interventions were considered when bleb leakage showed no signs of improvement after 1 month of conservative treatment. All patients in our study continued to have bleb leakage, whereas the rest had S2. Glaucoma medications were stopped. Standard conservative medical treatments included moxifloxacin (Vigamox; Alcon Canada Inc.) qid, atropine 1% (Isopto Atropine; Alcon Canada Inc.) bid, and aggressive surface lubrication. Three patients also failed bleb needling without MMC. As leakage persisted despite the above-mentioned therapy, CXL was performed at 12 ± 6.8 (1 to 47) months after its initial diagnosis. The average pre-CXL IOP was 3.9 ± 1.0 (1 to 7) mm Hg and the CDVA was 0.6 ± 0.2 (0.2 to 1.3). During CXL, only patient no. 2 had thick enough tissue to undergo deepithelialization.

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leakage despite medical management during 12 ± 6.8 (1 to 47) months and despite needling in 3. There were large variations for the duration of bleb leakages, increasing the heterogeneity of our studied group. One may argue that bleb leakage has a self-resolving tendency and that conservative treatment for 1 month may not be long enough. However, in our experience, if there are no signs of improvement after a whole month of conservative treatment, it is unlikely for the leakage to resolve spontaneously and it is reasonable to proceed with an alternative option to prevent leakage-related complications. In contrast, patients no. 1 and 5 demonstrated prolonged multifocal pinpoint leakages (27 and 47 mo, respectively) before the CXL treatment. The refractoriness and chronicity of the leakages in these 2 cases suggest the severity of tissue ischemia and friability. One may expect that including such cases may decrease the overall success rate of the CXL treatment. However, the Seidel test did normalize in these 2 patients, further supporting that CXL may be beneficial for the treatment of bleb leakage, even when it is chronic. In a study by Burnstein et al,\(^3\) while the nonincisional procedures offer 54% of initial leak closure, surgical bleb revision with conjunctival advancement remains the gold standard. With 71% of leakage closure and 57% of patients being hypotony free at final visit, practically speaking, CXL is an interesting option after conservative medical treatment or needling has failed. It is easy to perform and may spare patients risks associated with an incisional surgery.

Compared with pre-CXL measurements, CDVA was significantly better (\(P < 0.05\)) at all times. IOP was significantly higher (\(P < 0.05\)) at post-CXL 1 to 2 months and 3 to 6 months and showed a tendency (\(P = 0.06\)) of improvement at final visit. This lack of significance may be explained by the insufficient power due to the small number of observations. Of note, despite the normalized Seidel tests in the 2 patients with chronic multifocal pinpoint leakages, their IOP improvements were small and short lasting. We suspect that aqueous humor hyposecretion in these prephthisical eyes may be responsible for their persistent hypotony.

Collagen CXL is a mainstream treatment of corneal ectatic disorders by inducing covalent bonding between collagen molecules.\(^3\) It has also shown encouraging results in treating corneal edema and infectious keratitis.\(^5\) MMC-treated leaking blebs are known to contain little collagen.\(^14\) However, while the paucity of fibroblasts in leaking blebs renders tissue repair insufficient, 75% of these blebs demonstrated fibrovascular growths at their margin.\(^14\) We hypothesize that CXL of a leaking bleb reinforces residual collagen bonding and may also stimulate residual fibroblasts to secrete extracellular matrix to enhance the bleb’s tensile strength.

There is a large body of literature on the use of CXL in corneal ectatic disorders, and the protocol parameters (riboflavin concentration, UV light wavelength, irradiation intensity, and time) at our institution stem from these data. Riboflavin, a photosensitizer that induces oxygen radicals upon exposure to UV light, was found to have a large absorption coefficient at the concentration of 0.1% so that 90% of the UV radiation occurs in the stroma, whereas deeper structures including the endothelium remain protected.\(^15\) As the intact epithelium represents a barrier to riboflavin diffusion, the standard corneal CXL treatment requires removal of epithelium and instillation of riboflavin solution onto the deepithelialized cornea 20 to 30 minutes before radiation for optimal absorption.\(^16\) There have also been reports of experimental “epithelium-on” CXL treatment where the permeability of epithelium is increased through different methods.\(^5\) A wavelength of 365 nm is chosen for CXL treatment because, at this wavelength, riboflavin demonstrates its absorption maximum to achieve 90% absorption of the UV light in a 400-μm-thick deepithelialized cornea without damaging the endothelium or the lens.\(^17\) Because of the large absorption coefficient of riboflavin in the stroma, at the radiation strength of 3 mW/cm², the irradiation intensity is decreased enough at the endothelium that the exposure remains below the damage threshold.\(^18\) Finally, when collagen is exposed to an irradiance of 3 mW/cm² between 5 and 60 minutes, 30 minutes of irradiation time was found to yield the optimal biochemical effect.\(^19\) A significant biochemical stiffening occurs after 15 minutes of irradiation and reaches a plateau after 45 minutes. Even though all these parameters are deemed to be safe in a 400-μm-thick deepithelialized cornea and that none of our patients were known to have keratoconus, we took the precaution to prevent CXL of the cornea by holding a shield over it during the UV light exposure time.

Surface deepithelialization optimizes stromal diffusion of riboflavin during corneal CXL and increases its biomechanical effect.\(^16\) In our study, with the exception of patient no. 2, all other patients had blebs that were too thin to undergo deepithelialization safely. All had immediate improvement though effects were not long lasting in some (Table 1). Given the small number of observations, it is difficult to compare deepithelialized to “epithelium-on” CXL for treatment of bleb leakage. However, it is reasonable to speculate that CXL is more effective on a deepithelialized leaking bleb, though an epithelial debridement may be too risky in these eyes. Another potential avenue to explore is to inject a small amount of riboflavin into the bleb before CXL. This method was not performed in our patients for fear of potential toxicity related to penetration of riboflavin into the anterior chamber.

Shortcomings of our study include small sample size and lack of a control group. The self-resolving tendency of bleb leakage may be confounding though all patients underwent medical treatment for 12 ± 6.8 (1 to 47) months before CXL. Despite the absence of observed adverse events, we are aware of the potential complications following corneal CXL treatment reported in the literature.\(^20\) Finally, our hypothesis on CXL’s effect on fibroblasts in blebs requires validation by future studies.

In conclusion, collagen CXL is a noninvasive intervention offering good initial leakage closure and reasonable IOP and CDVA improvement in patients with late-onset bleb leakage. It is an interesting second-line option that can be performed after or combined with other conventional nonincisional treatments and may spare patients invasive surgical bleb revision.

REFERENCES