Review Article

Avascular Blebs and Late Bleb Leakage; A Review of Causes and Management

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Abstract

Trabeculectomy with mitomycin-C remains the gold standard for surgical glaucoma management; however, this technique includes some sight-threatening complications like avascular thin bleb, subsequent leakage and ultimately endophthalmitis. To date, various non surgical methods have been reported for the management of bleb leakage, but surgical management frequently becomes necessary especially in frank leakages. The most common surgical approach includes excision of the avascular and necrotic leaking bleb combined with the advancement of adjacent healthy conjunctiva. The aim of the present review is to discuss avascular bleb and late bleb leakage after trabeculectomy including their histopathology, risk factors, prevention and management.

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Introduction

The ultimate goal of trabeculectomy is the prevention of glaucomatous optic neuropathy progression through intraocular pressure (IOP) reduction and without development of hypotony [1]. This result is achieved via a diffuse filtering bleb formation best made by a fornix-based conjunctival flap rather than limbal-based techniques [2].

Mitomycin C (MMC), an antimetabolite agent isolated from Streptomyces Caespitosus, prevents DNA synthesis and reduces the chance of fibrosis [3]. Although it has been widely used during trabeculectomy to prevent fibrosis and increase surgical success, it serves as a double sword that can produce thin and avascular blebs with ischemia and leakage as the possible inadvertent consequences [4-10].

A large avascular area of the bleb is the most common predisposing factor for late bleb leakage compared with a cystic bleb [11]. Moreover, most avascular blebs show avascularity within the first postoperative year with the anterior location to be the most common site [12]. An avascular bleb could result in the late-onset bleb leakage months to years after trabeculectomy, which is directly proportional to the duration of avascularity [11,13-19]. Bleb leakage increases the risk of bleb-associated blebitis and endophthalmitis up to 26 folds, as the most catastrophic event after trabeculectomy [20]. In a study by Wolner et al., [21] 62 percent of the patients with bleb-related endophthalmitis had chronic and intermittent leakage. Interestingly all these patients had thin-walled blebs [21]. The incidence of late-onset bleb leakage after trabeculectomy with adjunctive antimetabolites varies between 1.8 % and 12.9 % [10, 22-24].

Conjunctival epithelial defect mainly predisposes the underlying bleb to frank late-onset bleb leaks [25]. The possible mechanism is a higher chance of aqueous oozing through the unhealed epithelial defect that can eventually deteriorate into an obvious point leakage [25]. Moreover, avascular blebs can cause potentially sight-threatening hypotony-related complications including flat anterior chamber, peripheral anterior synechiae, cataract, choroidal detachment and hypotonic maculopathy [10, 26-31].

The aim of the present review is to discuss avascular bleb and late bleb leakage after trabeculectomy including their histopathology, risk factors, prevention and management.

Methods

A PubMed and Google scholar search was performed, analyzing all publications from 1970 to 2018 regarding the topic "avascular bleb and late-onset bleb leakage" using keywords: bleb, late onset, leakage, avascular, and hypovascular. Only studies published in English language were included for this review.

Histopathology

Studies investigating histopathological characteristics of avascular blebs show the presence of irregular conjunctival epithelium, multiple breaks in the basement membrane, irregularly arranged collagen with few fibroblasts and lack of vessels in the substantia propria [6, 32-34]. Furthermore, the electron microscopy study of avascular blebs shows microvilli at the superficial area in some parts of the conjunctival epithelium [6]. Late-leaking blebs also contain focal epithelial thinning and interruption, hypocellularity, and stromal collagen degeneration [10].

Risk factors

The prevalence of bleb leakage among patients undergoing trabeculectomy with antimetabolites is estimated to be from 1.3 %

to 25 % [14, 35-38]. Avascular bleb formation is more frequent in a limbus-based conjunctival flap compared with a fornix-based flap [2, 39]. Excessive and sustained aqueous filtration is another risk factor for this complication [34, 40]. Conversely, a diffuse vascularized bleb with wide posterior extension decreases the risk of bleb failure and leakage [24]. Another mechanism causing bleb avascularity is the formation of a localized bleb with subsequent increase in the internal pressure of the bleb [34].

Prevention

There is no exact method to prevent the bleb avascularity [40]. Replacing MMC with another agent to lower complications has been tried in various studies. Nilforoushan et al., [41] compared Bevacizumab with MMC in trabeculectomy and showed similar complication rates between the two drugs and higher postoperative glaucoma medications needed in the Bevacizumab group. In two other studies, the same author investigated combined use of trabeculectomy and OculusGen implanted under the bleb and reported that this method was safe but still required higher glaucoma medications compared to MMC-trabeculectomy [42, 43].

Okuda et al., [40] found that application of a biodegradable, honeycomb-patterned film reduces bleb avascularity without affecting filtration surgery success rate in rabbits undergoing trabeculectomy with MMC by avoiding conjunctival exposure to excess filtrated aqueous [40].

Management

A thin avascular bleb can be closely followed. Various alarm signs including the presence of a shallow anterior chamber, reduced visual acuity, development of hypotony maculopathy, choroidal detachment and more importantly frank bleb leakage necessitate treatment [12, 18]. Bleb leakage needs special attention because of increased risk of endophthalmitis besides other hypotony related complications [13, 14, 21, 38, 44-46]. The ultimate goal of bleb leakage treatment includes the elimination of leakage as well as preserving filtration bleb function [47].

Conservative Management

Multiple modalities have been used for conservative management of bleb leakage including sodium hyaluronate and autologous serum eye drop [25], vigorous treatment of concomitant dry eye [1,48], suppressants of aqueous humor production [49], bandage contact lenses [49,50], tissue adhesives [50-54], induction of an inflammatory healing response in the bleb with chemical irritants [53], and symblepharon rings [55].

Surgical Management

Several techniques for surgical management of a leaking bleb have been reported with most of them reserved as the last resort. However, the surgical approach becomes necessary in many patients. These approaches include covering the leakage area with an overlying conjunctival flap [56-58], external conjunctival cryopexy [59], thermal coagulation by cautery [60], application of argon laser [61], collagen crosslinking (CXL) [62,63], direct suturing of the conjunctival defect (so-called buttonhole) [64,65], patching the sclerostomy site with a corneal [66] or scleral tissue [41,67-69], advancing a flap of Tenon's capsule from the superior fornix to plug the leakage area [56, 57, 70], surgical revision with the advancement of fornix conjunctival flap [5, 46, 65, 71, 72], free conjunctival autograft from either the same or the fellow eye [73], compression sutures [74], intra bleb autologous blood injection [75, 76], reconstruction with preserved human amniotic membrane for the

repair of difficult bleb leaks [51, 77], and bleb needling techniques [78].

Direct manipulation of a thin avascular bleb can cause traumatic damages to a semi-destroyed area that can worsen the bleb leakage. Thereby bleb revision surgeries are often considered as the last option to avoid bleb failure [79].

Regarding chronic leakages, there is often an epithelial tract that originates from bleb's surface entering into the episclera. To eliminate the leakage, this tract must be completely excised [31]. Since the leaking area is usually surrounded by a thin tissue, most of these procedures might be complicated by more damage to the bleb [49].

Currently, the most recommended surgical technique is excision of the leaking area of the bleb and the advancement of a fornix-based conjunctival flap made through undermining the surrounding conjunctiva combined with the widespread use of relaxing incisions to avoid a tight flap [46, 65, 71, 72]. In this technique, the anterior margin of the flap is sutured into the cornea. Nevertheless, 44 % to 86 % of patients undergoing bleb repair will require glaucoma medications for IOP control [79].

Discussion

Intraoperative antifibrotic agents like MMC are routinely used in trabeculectomy [28]. The main drawback of their usage is the increased risk of avascularity and thinning of the blebs. The risk of late bleb leakage is 3 times higher with the application of MMC compared with 5-fluorouracil [1]. Some blebs will become progressively thin, oversized, and vulnerable; therefore they are at risk of recurrent leakages and over filtration [6, 10]. Moreover, the 5-year risk of bleb related endophthalmitis, the most terrible complication of trabeculectomy, is increased up to 23 % after bleb leakage [9, 80].

Conjunctival epithelial defect predisposes bleb to frank late-onset bleb leaks through chronic aqueous oozing [31]. Therefore, maintaining an effective tear film is crucial for inhibiting a possible progression of epithelial defect into a dangerous bleb leakage [25]. Ophthalmologists should distinguish frank leakage containing an obvious site from bleb sweating as areas of pinpoint transconjunctival flow since the latter usually is not correlated with severe complications [6].

Many medically treated leaking blebs finally recur after conservative managements like the use of sodium hyaluronate and autologous serum [6,25, 31]. In longstanding leakages, the development of an epithelial tract in the leaking area would complicate the medical management and necessitates the surgical approach [21, 25]. The use of prophylactic topical antibiotics to minimize the risk of endophthalmitis is a controversial issue because of the increased risk of bacterial flora resistance that could result in a more aggressive infection [24].

Excision of the leaking area followed by the advancement of a conjunctival flap is the most recommended surgical approach [46, 65, 71, 72]. To prevent the development of a tight or small flap, some surgeons replace the excised necrotic area with a free conjunctival graft borrowed from ipsilateral side or the fellow eye [47]. These surgical modalities all share the risk of bleb failure [49]. van de Geijn et al., [79] in a retrospective study of 36 cases, reported three failed filtering blebs within 1 month and 2 more cases within 1 year after surgery because of subconjunctival and episcleral scarring. Complete and qualified success rates in their study were 51.6 % and 86.1 %, respectively and failed cases finally underwent re-trabeculectomy [79]. One eye was complicated with conjunctival and Tenon flap dehiscence and one eye was affected by

conjunctival wound leak at the limbus which underwent suturing [79]. Avascular leaking bleb recurred in one eye 19 months after surgery [79]. In a retrospective study Al-Shahwan et al., [81] studied 34 eyes that underwent bleb excision with conjunctival advancement for late bleb leakage after trabeculectomy and achieved IOP control without medication in 58.8 % of the operated eyes. Early leakage, late recurrent or persistent leakage, and endophthalmitis occurred in 7, 1 and 1 cases, respectively [81].

Lee et al., [82] in a retrospective review of 17 eyes undergoing avascular bleb excision with conjunctival advancement reported a success rate of 100 % with IOP between 6 and 18 mmHg with or without medication at 51 months of follow up. They reported relapse with perforation of the avascular area in one case 89 months after surgery [82]. Blepharoptosis occurred in 23 % of their cases in whom spontaneous resolution was finally achieved and only one case with sustained hypertropia occurred [82].

Budenz et al., [83] compared amniotic membrane transplantation with conjunctival advancement for the repair of late-onset bleb leakage and reported seven failures in the amniotic membrane transplant group versus no failure in the conjunctival advancement group. Of those seven patients with failures, two had persistent leaks that were unresponsive to further suturing, two had late-onset leakages, and three required repeated glaucoma surgery [83]. The cumulative survival for amniotic membrane transplant was 81 % at six months, 74 % at one year, and 46 % at two years, compared with 100 % in conjunctival advancement group [83]. Complications of bleb excision with conjunctival advancement include postoperative IOP spike, bleb leakage recurrence, bleb dysesthesia, filtering bleb failure, blepharoptosis, and hypertropia [84-87]. Nevertheless, this procedure seems to be the best surgical treatment for complicated avascular blebs that need an operation [47].

Conclusion

Avascular bleb and its potential complications should be assessed at each visit after trabeculectomy. Early detection may increase the chance of success for conservative treatments. Ophthalmologists should rigorously follow cases that are at risk for bleb associated infections including patients with frank leakage and should use surgical modalities to prevent potentially catastrophic sight-threatening events.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present study.