

Clinical Characteristics and Outcome of Bleb-Related Infection in Glaucoma Patients

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ABSTRACT

Objective: To study the clinical characteristics, causative organism, treatment, and clinical outcomes of bleb-related infection.

Materials and Methods: The medical charts of patients who were diagnosed with bleb-related infection, including blebitis and bleb-related endophthalmitis (BRE), from September 2001 to December 2019 at Siriraj Hospital were reviewed. The patients' demographic data, clinical characteristics, microorganisms found, treatment, and clinical outcomes were explored.

Results: We found a total of 42 eyes from 41 patients had been diagnosed with blebitis (11 eyes) and BRE (31 eyes) over the 18-year study period. More than 80% of the patients had experienced pain and redness as the presenting symptoms. The most common bleb characteristic in BRE was purulent bleb (74.2%), while in blebitis it was bleb injection (45.5%). Bleb leakage was documented in 27.3% and 22.6% of patients with blebitis and BRE, respectively. Among the 41 patients, 10 had a history of minor trauma before the onset of infection, such as a rubbed eye, foreign body entering into the eye, water splashed into the eyes, or the eyes had been washed with soap. The yield of vitreous culture in bleb-related endophthalmitis was 48.3%. The most common microorganisms were *Streptococcus spp.*, *Enterococcus spp.*, and *Haemophilus Influenzae*. Generally, the treatment for blebitis at our institute is broad spectrum topical and systemic antibiotics, while intravitreal broad spectrum antibiotics are added to the treatment regimen for BRE patients. For BRE in our cohort, 11 eyes required vitrectomy and 7 eyes had undergone bleb excision. Treatment for blebitis tended to have a good visual outcome, with a stable visual prognosis for 9 out of the 11 eyes diagnosed with blebitis. However, most of the BRE eyes had a worsened visual outcome. *Enterococcus spp.* and *Haemophilus Influenzae* resulted in poor visual outcomes.

Conclusion: The clinical characteristics of bleb-related infection in our patients were pain and redness. One fourth of patients had a history of minor trauma to the eye. To prevent bleb-related infection, the importance of patient education after trabeculectomy should be highlighted. Patients with presenting symptoms and unwanted behavior that could result in bleb infection should be identified and receive treatment alongside education.

Keywords: Bleb infection; blebitis; bleb-related endophthalmitis; clinical; sign; symptom; outcome; predisposing behavior; trauma, patient education (Siriraj Med J 2022; 74: 555-561)

INTRODUCTION

Trabeculectomy is the standard glaucoma treatment and usually reserved as the last resort after intolerable

side effects or disease progression become apparent despite the administration of the maximum tolerable topical medications. Glaucoma shunt surgery can cause

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decrease number of endothelial cell count⁴ as a long term complication. Trabeculectomy which appear to be safer for endothelial but the most serious complication of trabeculectomy is bleb-related infection. Even though, the incidence of bleb-related infection is rare at only 0.4–0.6%,^{1–10} such infection could lead to permanent visual loss and disability. Most studies divide bleb-related infection into two categories depending on the location of the infection: blebitis, which is infection of the bleb and is localized in the anterior segment, and bleb-related endophthalmitis, which is an infection of the bleb and entire globe.

The understanding of the disease presentation, risk factors, causative organism, and outcome of treatment is important to prevent a disastrous outcome of bleb-related infection. The most common causative organisms of bleb-related infection are *Streptococcus spp.*, *Staphylococcus spp.*, *Haemophilus influenzae*, and *Enterococcus spp.*^{9,11,12} Blebitis is usually treated with intensive topical antibiotics.⁶ The treatment of bleb-related endophthalmitis usually involves intravitreal antibiotics injection, mostly vancomycin and ceftazidime, although pars plana vitrectomy is performed as an alternative approach in some cases.^{6,11,12} The visual outcomes of bleb-related endophthalmitis have been reported as: improved (50%), declined (24%), and remained the same (26%).¹² Previous studies found that the risk factors of bleb-related infection were the use of anti-fibrotic agents, such as mitomycin-C or 5-fluorocil^{3,9,10,13,14}; inferior bleb approach^{10,11,13,15}; fornix-based conjunctival flap¹⁶; bleb leakage^{1,6,11,17,18}; bleb manipulation^{11,19}, such as bleb needling; and underlying diseases, such as diabetes²⁰ and blebitis.²⁰

Even though trabeculectomy is not an uncommon surgery in the Southeast Asia region in terms of the number of procedures at 122.6–234.0 procedures/1 million persons/year²¹, the lack of studies on bleb-related infection is still a problem. Moreover, differences in educational background, personal hygiene, culture, and healthcare accessibility can result in different courses of the disease, as reported in previous studies conducted in other regions. The clinical and microbiological characteristics of bleb-related infection can help guide the ophthalmologist to provide better patient education for improving long-term care regarding post-operative infection prevention and early diagnosis.

Therefore, the primary outcome of this study was to study the symptoms and signs of bleb-related infection. The secondary outcomes were to study the risk factors, causative organism, treatment, and outcome of treatment of bleb-related infection in Siriraj Hospital, Thailand.

MATERIALS AND METHODS

Before we reviewed the medical records, approval for the study was obtained from the Siriraj Institutional Review Board committee, Siriraj Hospital, Mahidol University. We searched the Siriraj Hospital coding database for all patients who were diagnosed with blebitis or bleb endophthalmitis or both. We retrospectively reviewed the records of the patients who were diagnosed with blebitis or bleb-related endophthalmitis or both by diagnosis or by referral to Siriraj Hospital and who were treated at Siriraj Hospital between September 2001 and December 2019. Patients who had a controversial diagnosis of bleb-related infection were excluded from this study. Blebitis was defined as a presumed bleb infection in an eye after filtering surgery when the vitreous was not clinically involved.² Bleb-related endophthalmitis was defined as an infection invading the anterior chamber and eventually passing into the vitreous.² The patients' demographic data, trabeculectomy procedure, co-ocular diseases, diagnosis of glaucoma, management of post-trabeculectomy, signs and symptoms, specimen culture, treatment of bleb-related infection, and outcome of the treatment were reviewed. Stable visual acuity means visual acuity is not deteriorated by more than 2 lines of the Snellen chart or changed from hand movement to the projection of light.

Descriptive statistics were used to evaluate the patients' baseline demographic data, location of the bleb approach, the use of anti-fibrotic agents, type of glaucoma, signs and symptoms of bleb-related infection, the causative microorganism from the culture, type and route of treatment, visual outcome, and post-infection glaucoma status.

RESULTS

After a review of 18 years' medical records, 42 eyes of 41 patients were identified as having been diagnosed with bleb-related infection. The patients' demographic data are shown in Table 1.

The average age at the time of bleb-related infection presentation was 58.5 years old (range 5–87 years old). Seventy-three percent of the patients had bleb endophthalmitis. Nearly a half of patients (47.6%) had underlying primary open angle glaucoma (Table 1).

Symptoms and signs

Blebitis

As shown in Table 2, the most common ocular symptom was redness in 8 eyes (72.7%) follow by pain in 54.5% of patients. All the blebitis patients had conjunctival injection followed by an injected bleb in 45.5% of patients.

TABLE 1. Patients' demographic data.

Demographic data	Number (42 eyes, 41 patients)
Sex	
Male	29
Female	12
Side	
Right	20
Left	22
Age (when BRI; years old)	58.5 (range 5-87)
Diagnosis BRI	
Blebitis	11
Bleb-related endophthalmitis	31
Diagnosis of glaucoma	
POAG	20
PACG	4
Secondary glaucoma	9
JOAG	3

TABLE 2. Signs and symptoms of BRI.

Signs and symptoms	Blebitis (11 eyes)	BRE (31 eyes)
Symptoms		
Pain	6 (54.5%)	28 (90.3%)
Redness	8 (72.7%)	27 (87.1%)
Discharge	6 (54.5%)	20 (64.5%)
Tearing	4 (36.4%)	9 (29%)
Signs		
Conjunctival injection	11 (100%)	31 (100%)
Bleb leakage	3 (27.3%)	7 (22.6%)
Bleb purulent	4 (36.4%)	23 (74.2%)
Bleb injection	5 (45.5%)	7 (22.6%)
Anterior chamber reaction	10 (90.9%)	31 (100%)
Hypopyon	1 (9.1%)	20 (64.5%)
Mild cells	4 (36.4%)	2 (6.45%)
Marked cells	6 (54.5%)	29 (93.6%)
Flare	0	5 (16.1%)
Plasmoid	2 (18.2%)	18 (58.1%)
Fundus examination		
Normal fundus examination	9 (81.8%)	0
Mild anterior vitreous cells	1 (9.1%)	4 (12.9%)
Marked anterior vitreous cells	0	6 (19.3%)
Obscuration due to anterior segment	1 (9.1%)	21 (67.7%)

Almost all the patients (91%) had an anterior chamber reaction, with 54.54% of patients having marked anterior chamber cells. The only patient who didn't have an anterior chamber reaction had purulent bleb. Most of the blebitis cases had normal fundus (81.8%).

Bleb-related endophthalmitis

In contrast to blebitis, 90.3% of patients presented with pain. All the patients had conjunctival injection followed by purulent bleb in 74.2% of patients. Overall, 93% of BRE patients had marked anterior chamber cells with 64.5% of BRE patients having hypopyon. More than half (64.5%) of the patients had obscured fundus (64.5%) (Table 2).

Events

Most the bleb-related infection patients did not have a history of any trauma before. However, two patients had rubbed the affected eye before they were diagnosed as *Enterococcus* BRE. Three patients had a history of a foreign body in the affected eye, such as dust or an insect. The vitreous culture results of these three patients were *Haemophilus*, *Streptococcus*, and *Staphylococcus*. Two patients had a history of water spreading into the affected eye, with one occurring while cooking and another while praying. One patient had stabbed her finger in the affected eye while washing her face, and another patient had washed the affected eye with soap after eye irritation.

Underlying diseases

The most common underlying diseases found in bleb-related infection were diabetes mellitus in 12/41 patients (29.3%, Blebitis 6/11 BRE 6/31) and hypertension in 20/41 patients (48.8%).

History of trabeculectomy procedure

The trabeculectomy site, intraoperative use of anti-fibrotic agents, and types of conjunctival flap and bleb manipulations are shown in Table 3. None of the recorded eyes with trabeculectomy had any other surgery combined or intraoperative complications. Only one eye needed long-term (10 months) topical steroid use after trabeculectomy due to co-morbid ocular disease (chronic anterior uveitis). No long-term topical antibiotics were used.

Bleb manipulations, including 5-fluorouracil subconjunctival injection and bleb needling, were done more than 4 months before the bleb-related infection. There was no history of glue application or tissue plasminogen activator injection before bleb-related infection in our institution.

TABLE 3. History of trabeculectomy and bleb characteristics in BRI patients.

Characteristics	Number (42 eyes)
Trabeculectomy procedure	
Bleb location	
Superior	39
Inferior	3
Intraoperative anti-fibrotic agent used	
Mitomycin-C	26
5-Fluorouracil	1
No use of any anti-fibrotic agent	2
No recorded data	13
Type of conjunctival flap	
Fornix-based conjunctival flap	16
Limbal-based conjunctival flap	11
No recorded data	15
Bleb manipulation	
Needling	6
5-Fluorouracil injection	12
Contact lens wearing	4
Re-suture bleb	4
Autologous blood Injection	2
Bleb revision	1
Bleb characteristic before BRI	
Bleb leakage	11
Cystic bleb	18
Avascular bleb	19
Thin wall bleb	7
Overhanging bleb	1
Flat bleb	2

In BRE patients, 13 eyes had fornix-based conjunctival flap while 7 eyes had limbal-based conjunctival flap with 11 eyes with no record of conjunctival flap type.

The mean duration from trabeculectomy to bleb-related infection was 65.4 months (range 0.33-192.0 months). The characteristics of the blebs before infection are shown in Table 3, with the most common being avascular bleb (55.9%) followed by cystic bleb (52.9%) and bleb leakage (32.4%) There was no characteristics of tense and opaque blebs in the bleb-related infections.

Organisms

Blebitis

The eye discharges from three eyes were sent for culture and the results were *Staphylococcus spp.* for two

eyes and no growth of culture for one eye. The aqueous fluid of three eyes and vitreous of four eyes were sent for analysis and no growth was reported for all (Table 4). There was one eye which both eye discharge and aqueous were sent for culture. The result came back with *Staphylococcus spp.* from eye discharge.

Bleb-related endophthalmitis

In 29 out of a total of 31 eyes with bleb-related endophthalmitis, there was a 48.5% positive rate from the vitreous cultures, in contrast with blebitis, where the yield of the aqueous cultures was zero (Table 4). There were 9 eyes which the specimens were taken from both aqueous and vitreous. Three eyes had positive vitreous culture and 2 eyes had positive result from both specimens with the same causative agents.

Treatment

All the blebitis patients received topical antibiotics. The medication regimens were combined fortified vancomycin and fortified fortum in 5 eyes, combined fortified vancomycin and fortified amikacin in 3 eyes, and combined fortified cefazolin and fortified amikacin, topical levofloxacin, and topical moxifloxacin each in 1 eye. Five of 11 blebitis patients received subconjunctival antibiotics injection. The most common type of antibiotics was subconjunctival vancomycin and ceftazidime injection

for 4 cases. Meanwhile intracameral antibiotics injection was applied in only 3 patients. Five patients underwent intravitreal antibiotics injection, comprising combined vancomycin and ceftazidime. Systemic antibiotics were prescribed in 9 patients, including oral levofloxacin in 4 patients, clarithromycin in 2 patients, ofloxacin in 2 patients, and combined intravenous vancomycin and amikacin in 1 patient.

All the bleb-related endophthalmitis patients received topical antibiotics, comprising combined fortified vancomycin and fortified ceftazidime in 22/31 eyes (71%), combined fortified vancomycin and fortified amikacin in 7/31 eyes (22.6%), combined fortified cefazolin and gentamicin in 1 eye, and moxifloxacin in 1 eye. There were 16 and 8 eyes with bleb-related endophthalmitis that received subconjunctival and intracameral antibiotics, respectively. Additionally, 11 eyes underwent vitrectomy. Intravitreal antibiotics were injected in 27 eyes, with the most common being combined vancomycin and ceftazidime in 21 eyes, followed by combined vancomycin and amikacin in 3 eyes, combined vancomycin–ceftazidime–amikacin in 1 eye, combined amikacin and clindamycin in 1 eye, and cefazolin in 1 eye. Most bleb-related endophthalmitis patients were prescribed systemic antibiotics (30 eyes), including combined vancomycin and ceftazidime in 15/30 (50%), and oral levofloxacin in 7/30 (23.33%). Bleb excision was performed in 7 eyes.

TABLE 4. Culture result from various specimens.

Specimen	Blebitis	Bleb-related endophthalmitis
Discharge culture		
<i>Staphylococcus spp.</i>	2	-
No organism found	1	2
Aqueous culture		
<i>Streptococcus spp.</i>	-	1
<i>Haemophilus Influenzae</i>	-	1
<i>Acinetobacter spp.</i>	-	1
No organism found	3	7
Vitreous culture		
<i>Streptococcus spp.</i>	-	5
<i>Enterococcus spp.</i>	-	3
<i>Haemophilus Influenzae</i>	-	3
<i>Staphylococcus spp.</i>	-	1
<i>Morexella spp.</i>	-	1
<i>Candida spp.</i>	-	1
No organism found	4	15

Outcomes

Blebitis

The visual acuity outcome in all eyes after blebitis had subsided was the same as that at baseline before infection. By converting visual acuity to logMAR unit, there was no difference between pre- and post-blebitis. Pre-blebitis was 0.88 ± 1.500 and post-blebitis was 0.93 ± 1.497 . The glaucoma status was stable in 4 eyes without topical anti-glaucoma being added; however, 3 eyes needed more topical anti-glaucoma after the infection to control the disease, and 4 eyes proceeded toward needing penetrating glaucoma surgery.

Bleb-related endophthalmitis

The visual acuity after the treatment of bleb-related endophthalmitis after 1 year was stable in 9 eyes, but deteriorated by more than 2 lines of the Snellen chart or changed from hand movement to the projection of light in 16 eyes. Using logMAR visual acuity, there was significant deterioration of visual acuity after bleb related endophthalmitis (Mean difference -1.66 ± 1.837 95% CI -2.422 to -0.906 p-value = 0.00). Before BRE logMAR visual acuity was 0.57 ± 0.723 compare to 2.24 ± 1.888 after the event. The glaucoma status progressed in 27 eyes, including to phthisis bulbi in 13 eyes (42%).

DISCUSSION

This was a study of 42 bleb-related infection cases over 18 years since the first electronic medical records were implemented at the Medical Educational Center, Siriraj Hospital.

Our results showed that pain and redness were the most common ocular symptoms of bleb-related infection. Meanwhile, conjunctival injection was found in all cases of bleb-related infection. Severe anterior chamber reactions (e.g., marked anterior chamber cells, hypopyon, and plasmoid reaction) were reported frequently in bleb-related endophthalmitis. Fundus examination was also hardly performed in bleb-related endophthalmitis. The most common bleb characteristic in bleb-related endophthalmitis was purulent bleb, supported by a “white-on-red” appearance. Most the bleb-related infection patients did not have any history of ocular trauma. However, 24% of the bleb-related infection cases had a history of ocular trauma. There were 2 patients with a history of eye rubbing who were diagnosed with *Enterococcus* bleb-related endophthalmitis. It is known that *Enterococcus spp.* can be found in the gastrointestinal tract of humans, and these endophthalmitis cases indicate low hygiene activities. Patients who had a history of water spreading to the eyes had culture negative organisms or

low-virulence organisms (*Morexella spp.*). Nobody had a history of infection from swimming. Some activities reflect insufficient self-care in post-trabeculectomy.

Lehmann reported diabetes was the main risk factor of bleb-related infection.³ The prevalence of diabetes in patients aged 45-54 years old in Thailand was 9.8%.⁴ Diabetes was present in 13% of glaucoma patients.⁵ Our first finding reported diabetes in bleb-related infection in 29.3% of cases, which was higher than the prevalence of diabetes in glaucoma patients. Our second finding showed that mitomycin-C was used in 61.9% of procedures. Many studies have found mitomycin-C to be associated with bleb-related infection.^{3,6-10} However, recent practice has shifted to mitomycin-C rather than 5-FU. This might result in more percentage of bleb infection in patients who had used mitomycin-C to augment trabeculectomy. Therefore, it was difficult to interpret the association of mitomycin-c use with bleb-related infection. Evidence of chronic blepharitis,¹¹ the presence of nasolacrimal duct obstruction,¹² and fornix-based conjunctival flap⁹ were associated with bleb-related infection. However in our study there was not enough number of eyes and lots of missing data to concluded that fornix-based conjunctival flap is associated with bleb related infection. From previous studies fornix based conjunctival flap as a risk factor of having bleb related infection is still controversy.¹³ The number of the eyes having fornix based conjunctival flap is greater which may result from the recent prefer practice of flap type.

In term of other possible risk factors in this study, we did not find any history of other ocular diseases except conjunctivitis in our bleb-related infection study. Keep in mind that this finding is one of the limitations in this study due to retrospective nature which result from the completeness of medical record. Bleb manipulation was reported as a risk factor of bleb-related infection.^{12,14} Our findings demonstrated that no bleb-related infection occurred after recent (< 1 month) bleb manipulation. We found that the most common bleb characteristics were cystic and avascular blebs. This could be explained by the thin wall of cystic blebs or micropores, which may allow microorganisms to get into the bleb leading to bleb-related infection.

Previous studies have found *Streptococcus spp.* and *Staphylococcus spp.*^{8,12,15,16} to be causes of bleb-related endophthalmitis. The causative organisms of bleb-related endophthalmitis in our study were not only *Streptococcus spp.*, but also *Haemophilus Influenzae*, and *Enterococcus faecalis*. In the *Enterococcus* bleb-related endophthalmitis eyes, the patients all had a history of avascular cystic bleb. In the eyes with both aqueous and vitreous specimens

were taken, the positive result have found in vitreous cultures. Therefore it supported that vitreous culture had important role in diagnosing BRE.

Blebitis had a better visual outcome than bleb-related endophthalmitis in our subjects. There was a stable visual outcome in bleb-related endophthalmitis in 9 eyes, with no organism identification in the culture of 6 eyes. The visual outcome in all our *Enterococcus* bleb-related endophthalmitis cases was no light perception, ending up in phthisis bulbi. Therefore, patients with a history of rubbing eyes should be wary of *Enterococcus* bleb-related endophthalmitis. Also, once *Enterococcus* bleb-related endophthalmitis is diagnosed, aggressive and urgent treatment must be delivered and the possible visual outcome should be forewarned to patients. Most importantly, patient education about appropriate self-care after trabeculectomy should be highlighted, particularly regarding eye rubbing and the need for eye protection when doing activities with a high risk of water, dust, or foreign bodies ingress into the eye.

The key limitation of our study to note is the retrospective study design. Bleb-related infection is a rare trabeculectomy complication, thus resulting in a small sample size. However, we reported almost all the aspects and cases of bleb-related infection in our tertiary care medical center in Thailand, which could be beneficial in terms of ensuring patient education to prevent bleb-related endophthalmitis. The symptoms, clinical signs, prognosis, and treatment regimen can present a gross picture for the ophthalmologist to be able to better deal with the bleb-related infection.

CONCLUSION

Bleb-related infection is a rare complication of glaucoma surgery. The clinical characteristics include pain and redness. One fourth of patients in our study had a history of minor trauma to the eye. Appropriate health education for glaucoma patients after trabeculectomy should be provided. Patients with presenting symptoms and unwanted behavior that could result in bleb-related infection should be identified and receive treatment alongside education.

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