

Incidence of bleb-associated endophthalmitis in the United States

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Purpose: To evaluate the 5-year incidence rate of blebitis and bleb-associated endophthalmitis in the United States.

Methods: In this retrospective cross-sectional study, we utilized a large commercial health insurance claim-based database during 2007–2011 and identified all patients who had a record of trabeculectomy in 2007. These patients were followed until the end of 2011. During the follow-up period, all incidences of blebitis, confirmed bleb-associated endophthalmitis, and presumed bleb-associated endophthalmitis were recorded. Kaplan–Meier survival analysis was utilized to calculate 5-year cumulative incidence rates of blebitis and bleb-associated endophthalmitis following trabeculectomy procedures.

Results: Among the 1,461 trabeculectomies included in our analysis, eight cases of blebitis, five cases of confirmed bleb-associated endophthalmitis, and eight cases of presumed bleb-associated endophthalmitis were identified. We found that the 5-year cumulative incidence of blebitis was 0.55%±0.19%. The 5-year cumulative incidence of bleb-associated endophthalmitis was 0.45%±0.2% when only confirmed cases were included and 1.3%±0.34% when presumed cases were also added to the analysis. The mean time from procedure to diagnosis was 45 months for blebitis and 33 months for bleb-associated endophthalmitis.

Conclusion: Blebitis and bleb-related endophthalmitis are uncommon in the United States. The 5-year cumulative incidence was 0.55% for blebitis and 0.45%–1.3% for bleb-associated endophthalmitis.

Keywords: bleb, blebitis, bleb-associated endophthalmitis, trabeculectomy

Introduction

Bleb-related infections are potentially sight-threatening complications of trabeculectomy. These infections can be divided into two categories: blebitis and bleb-associated endophthalmitis. Blebitis refers to an infection limited to the bleb, with varying degrees of anterior chamber inflammation. When this infection moves beyond the anterior chamber and involves the vitreous, it is referred to as bleb-associated endophthalmitis.

Among bleb-related infections, endophthalmitis carries the highest risk of morbidity and is associated with poor visual outcomes. One study reported that 36%–62% of patients with bleb-associated endophthalmitis had a final visual acuity of worse than 5/200, even after treatment,¹ and other studies have reported that the incidence of no light perception ranged from 23% to 35%.^{2,3} Several risk factors have been associated with bleb-associated endophthalmitis, including bleb leakage, use of antimetabolites, inferior trabeculectomy, thin avascular bleb, axial myopia, blepharitis, chronic antibiotic use, and younger age.^{4–9} While bleb-related endophthalmitis can occur acutely (<4 weeks), most cases are delayed onset (>4 weeks), with a reported average onset of 5 years after trabeculectomy.¹⁰ One study reported endophthalmitis 42 years after glaucoma filtration surgery.¹¹

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Numerous series have reported the incidence of bleb-associated endophthalmitis at between 0.17% and 13.2%.^{8,12–26} However, many of these reports were single center, potentially creating a bias with regard to location-specific surgical techniques, geographic variability of microorganisms, and patient demographics. In addition, with the exception of a small minority of the studies,^{15,24–26} most used relatively smaller sample sizes (<600 trabeculectomies), possibly affecting the validity of the statistical analysis. In addition, the use of adjuvant antimetabolites (ie, mitomycin C and 5-fluorouracil) may have led to increased rates of endophthalmitis.^{14,24,25} At the same time, surgical techniques and surgeon confidence in using intraoperative antimetabolites may have improved in recent years, and this warrants a re-evaluation of the incidence rates using a large sample size and adequate follow-up time. In this study, we aimed to utilize a large nationally pooled insurance claim-based database to calculate the cumulative incidence of bleb-associated endophthalmitis following trabeculectomy procedures and to characterize these patients.

Methods

Data source

The current study is a retrospective cross-sectional case series utilizing the MarketScan Commercial Claims and Encounters database and the MarketScan Medicare Supplemental and Coordination of Benefits outpatient services and inpatient databases (Truven Health Analytics, Ann Arbor, MI, USA) from 2007 to 2011 (the most recent year the databases were available to us). The MarketScan family of databases comprises the largest convenience-based proprietary database in the US, annually encompassing approximately 40–50 million patients with employer-sponsored or supplemental insurance. These databases consist of de-identified, individual-level health records (inpatient and outpatient) obtained from large employers, hospitals, and Medicare programs. The MarketScan database contains de-identified and anonymized records and complies with the privacy requirements of the Health Information Portability and Accountability Act of 1996 (HIPAA), so Institutional Review Board (IRB) approval was not required.

The MarketScan outpatient services databases include demographic, provider type, and insurance information along with up to four diagnosis codes and one procedure code per recorded insurance claim (coded using the International Classification of Disease [ICD-9] and Current Procedural Terminology [CPT], respectively). Again, the databases are fully de-identified and thus HIPAA compliant

and exempt from IRB approval. Detailed information regarding the structure, de-identification of patient records, and HIPAA compliance of MarketScan databases can be found elsewhere.²⁷

Study sample and statistical analysis

The overall objective of this study was to identify patients who had a record of glaucoma filtering surgery in 2007 and follow their medical records until the end of 2011. We utilized CPT codes to select all the patients with such a history of trabeculectomy (CPT codes 66170 and 66172) in the year 2007. As the MarketScan databases are insurance claim based, they provide medical records for only the period of time during which the patients had active insurance coverage. As such, to be able to capture complete and uninterrupted medical records of patients during our study's follow-up period, only patients with continuous medical insurance coverage from the date of their trabeculectomy to the end of 2011 were included.

All recorded medical diagnoses of these patients including blebitis (ICD-9 397.61 and 397.62) and bleb-associated endophthalmitis (ICD-9 code 379.63) were identified throughout the follow-up period. For the purposes of this study, we considered any patient with diagnosis code 379.63 to be a “confirmed” case of bleb-associated endophthalmitis. We also selected patients with ICD-9 diagnosis codes of 360.00 (“purulent endophthalmitis, unspecified”), 360.01 (“acute endophthalmitis”), and 360.02 (“panophthalmitis”) who did not have records of additional ophthalmic surgery, ophthalmic trauma, or history of intravitreal injection within 2 months prior to their endophthalmitis diagnosis. We hypothesized that these patients also represented cases of bleb-associated endophthalmitis that were incorrectly coded by their treating physicians, and for the purposes of this study, we considered these patients to be “presumed” cases of bleb-associated endophthalmitis.

Bleb revision procedures were identified by combined coding of CPT 66250 (“revision or repair of operative wound of anterior segment, any type, early or late, major or minor procedure”) along with any of the primary open-angle glaucoma ICD-9 diagnosis codes (365.10–365.15). Additional ICD-9 and CPT codes were queried to identify patients' comorbidities and procedures of interest.

We used descriptive statistics and cross-tabulations to evaluate prevalence estimates of comorbidities and demographic information. Kaplan–Meier survival analysis was utilized to calculate cumulative incidence of bleb-associated

endophthalmitis following trabeculectomy procedures. All statistical analyses were performed with SPSS (Version 22, SPSS Inc, Chicago, IL, USA).

Results

After excluding patients with noncontinuous insurance coverage during the follow-up period, utilizing CPT, 1,461 glaucoma filtering surgeries were included in this analysis. The age of included patients in this analysis ranged from infancy (<1 year old) to 95 years old with a mean of 68.9 ± 12.8 years of age. There were 685 males (46.9%) and 776 females (53.1%).

Among the 1,461 glaucoma filtering surgeries analyzed, 67.8% had CPT code 66170 ("trabeculectomy ab externo in absence of previous surgery") and the remaining 32.2% had CPT code 66172 ("trabeculectomy ab externo with scarring from previous ocular surgery or trauma – includes injection of antifibrotic agents"). The medical records of individuals were followed from the date of their glaucoma filtering surgeries in 2007 to the end of 2011, which yielded a mean follow-up time of 53.8 ± 3.4 months (4.5 years).

In the database, five recorded cases of confirmed bleb-associated endophthalmitis (ICD-9 code 379.63), eleven cases of presumed bleb-associated endophthalmitis, and eight cases of blebitis were identified. Three of the endophthalmitis cases had CPT code 66170, and the remaining two had a recorded CPT code of 66172. Utilizing only the confirmed cases of endophthalmitis, Kaplan–Meier analysis showed that the cumulative incidence of developing bleb-associated endophthalmitis was $0.45\% \pm 0.2\%$ at the maximum 5-year follow-up. The mean time to diagnosis of endophthalmitis following trabeculectomy was 44.6 months (or 3.7 years) and ranged from 23 months to 55 months.

In a separate analysis, eleven cases of presumed bleb-associated endophthalmitis were identified that were potentially miscoded as other categories of endophthalmitis for a total of 16 endophthalmitis cases. In this scenario, the 5-year cumulative incidence of presumed bleb-associated endophthalmitis was $1.3\% \pm 0.34\%$, and the mean time to diagnosis of endophthalmitis following trabeculectomy was 32.8 months (2.7 years), ranging from 6 months to 55 months (Table 1). Among all 16 cases of confirmed and presumed bleb-associated endophthalmitis, two (12.5%) had a record of prior blebitis and six (37.5%) had a record of bleb revision surgery. In patients with bleb-associated endophthalmitis, vitreous tap and intravitreal injection of antibiotics were used in 14 (87.5%) cases and pars plana vitrectomy was utilized in five cases (31%). Two bleb-associated endophthalmitis cases had no treatment records in the database (Table 1).

Additionally, 5-year cumulative incidence of blebitis was $0.5\% \pm 0.19\%$ with mean time to diagnosis of 45 months, ranging from 2 months to 47 months.

Discussion

Bleb-associated endophthalmitis is a serious complication of trabeculectomy. Prompt recognition and treatment of bleb-related infections are important for best possible clinical outcomes. Signs and symptoms of bleb-associated endophthalmitis are similar to other forms of endophthalmitis and most commonly include eye pain and decreased vision.²⁸ The presence of anterior chamber hypopyon and inflammatory cells in the vitreous are helpful in differentiating blebitis from endophthalmitis. Streptococcal species are the main causative agents for bleb-associated endophthalmitis in the US,^{2,10,11,28} while staphylococcal species are the predominant pathogens in East Asia,^{3,24} demonstrating a potential geographical variation.

Table 1 Characteristics of patients with bleb-associated endophthalmitis

Characteristic/patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
General																
Age, years	60	54	58	68	68	64	63	64	84	73	68	76	69	52	81	55
Sex	F	F	M	M	F	M	M	M	F	F	F	F	M	M	F	F
Follow-up time, months	50	52	56	50	55	52	58	53	51	49	57	55	58	59	21	54
Time to endophthalmitis, months	48	45	55	23	52	9	53	6	20	39	16	21	10	52	58	58
Blebitis prior to endophthalmitis	NR ^a	Yes	Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bleb revision surgery	Yes	NR	NR	Yes	Yes	NR	NR	NR	Yes	NR	Yes	NR	Yes	NR	NR	NR
Recorded treatments																
Intravitreal antibiotics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR
Topical antibiotics	Yes	Yes	NR	Yes	NR	NR	NR	NR	Yes	Yes	NR	NR	Yes	NR	Yes	NR
System antibiotics	NR	NR	NR	Yes	NR	Yes	Yes	NR	NR	NR	Yes	NR	Yes	NR	NR	NR
Vitrectomy	NR	NR	Yes	NR	NR	NR	Yes	NR	NR	Yes	Yes	Yes	NR	NR	NR	NR

Note: ^aThe first five columns indicate patients with a confirmed diagnosis of endophthalmitis, while the remaining patients have presumed endophthalmitis.

Abbreviations: F, female; M, male; NR, none recorded.

To date, there have been no established and official guidelines for the treatment of bleb-related infections. The Endophthalmitis Vitrectomy Study²⁹ did not recruit this cohort of patients, so its results do not directly apply to the management of these patients. Treatment regimens range from topical antibiotics for isolated blebitis to tap and inject or pars plana vitrectomy, depending on the severity of the infection. Furthermore, even with appropriate treatments, the final visual outcomes tend to be poor. A recent study found that close to half of the patients with bleb-associated endophthalmitis had final visual acuity of worse than 20/400, despite receiving the indicated medical or surgical therapies.¹ As a result, it is important to re-evaluate the incidence of bleb-related endophthalmitis using a large sample size and adequate follow-up time.

Previous studies have reported a wide range of cumulative incidence rates for the development of bleb-associated endophthalmitis. This variability in reported incidence rates may be due to differences in surgical techniques, sample sizes used in analyses, and the duration of follow-up times. As many of these studies worked with relatively small sample sizes and limited average follow-up times, we aimed to investigate bleb-associated incidence rates utilizing a large proprietary database that allowed us to follow patients' medical records for up to 5 years. To our knowledge, this was the first time that a large commercial database containing data from all 50 states was used to evaluate these incidence rates. We found that the cumulative incidence rate of bleb-associated endophthalmitis ranged between 0.45% and 1.3% at the maximum of a 5-year follow-up mark. These incidence rates fall within the spectrum of previously reported rates.

While our analysis included all cases of trabeculectomy with or without adjuvant chemotherapy, most of the prior studies that reported higher incidence rates focused solely on trabeculectomies that were accompanied by adjuvant mitomycin C or 5-fluorouracil injections.^{13,14,17,19,21–23,26} This may partly explain the higher incidence rates reported by those publications. While adjuvant antimetabolites such as mitomycin C and 5-fluorouracil have greatly increased the success rates of filtration surgeries, their use results in formation of thin and avascular blebs, potentially leading to easier migration of pathogens across the bleb and leading to higher rates of bleb-associated endophthalmitis.^{14,24,25} As the intraoperative use of these adjuvant antifibrotics is not coded separately and is included with the trabeculectomy procedural codes, we were unable to calculate the proportion of trabeculectomies in our sample size accompanied by adjuvant therapy.

Despite the higher rates of bleb-related infections in the first decade following the introduction of intraoperative antimetabolite use, these rates have declined significantly in more recent years,³⁰ which may also partly explain why our cumulative incidence rate utilizing a more recent data sample was lower than those of older publications. The drop in the incidence rate of bleb-related infections has been attributed to many factors, including increased surgeon confidence in using intraoperative mitomycin C, a shift toward limbus-based from fornix-based procedures, and use of a larger area for mitomycin C application.³⁰ Both fornix-based conjunctival flaps and a larger area for mitomycin C application may lead to less frequent formation of cystic blebs, an important risk factor for blebitis and bleb-associated endophthalmitis.^{31,32}

The current study has several strengths and limitations. For our analysis, this study utilized a large database that includes patients from all 50 states of the United States, which reduced the dependence of our results on location-specific variables (ie, patient demographics or preferred surgical techniques). In addition, the database allowed us to detect all patients' comorbidities and any new diagnoses (regardless of the specialty) throughout the follow-up period.

The major limitation of this study is the fact that there is no way to confirm the diagnosis of these cases. The MarketScan databases are insurance claim-based, and the medical diagnoses and surgical procedures are recorded as ICD-9 and CPT codes, respectively, so the accuracy of the data necessarily depends upon proper coding by the treating physicians. We assumed that any case coded with diagnosis 379.63 was a definite case of bleb-associated endophthalmitis, so we considered these "confirmed" cases. In addition, we assumed that any case coded with diagnoses 360.00, 360.01, or 360.02 was likely a miscoded case of bleb-associated endophthalmitis, so we considered these "presumed" cases. Because the databases are fully de-identified, there is no way to confirm the accuracy of these assumptions, and our data should be evaluated with this in mind. Furthermore, the current study is unable to evaluate clinical findings or morbidities that do not have specific diagnosis codes associated with them, such as bleb leaks, or identify the causative pathogens in individuals with bleb-associated endophthalmitis.

Conclusion

In conclusion, the cumulative incidence of blebitis was 0.55%, and the cumulative incidence of bleb-associated endophthalmitis was between 0.45% and 1.3% after up to 5 years of follow-up. To our knowledge, this is the first time that a large commercial claims database was utilized to

calculate these incidence rates. While it has been proposed than an increase in use of adjuvant antimetabolites would lead to an increase in overall incidence of bleb-associated endophthalmitis, the calculated rate was at the lower end of the spectrum of numbers reported by previous publications. This may have been partly due to improved surgical techniques over recent years.

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Disclosure

The authors report no conflicts of interest in this work.

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