

Risk factors for development of post-trabeculectomy endophthalmitis

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Abstract

Background/aims—Although adjunctive use of antiproliferative agents improves the success rate of glaucoma filtration surgery it profoundly alters the morphology of the filtering bleb. In view of these structural changes, which have been suggested to predispose to bleb infection, the relative importance of potential risk factors in the development of post-trabeculectomy endophthalmitis was investigated.

Methods—A case-control study was performed on patients with post-trabeculectomy endophthalmitis presenting to a single academic centre over a 6½ year period. Cases were diagnosed by the combination of vitreous and aqueous inflammation occurring 4 or more weeks postoperatively with control patients chosen by selecting the three patients undergoing trabeculectomy immediately following each index case.

Results—Analysis of these data, derived from 23 cases and 69 controls, demonstrated that an episode of blebitis and the presence of diabetes mellitus were statistically significantly associated with subsequent endophthalmitis (odds ratios (OR) 11.8, 95% CI: 2.21–88.31, $p = 0.003$ and OR 4.51, 95% CI 1.02–20.29, $p = 0.04$ respectively). The data also suggest an association exists between antiproliferative use and endophthalmitis (OR 3.3, 95% CI 0.95–15.19, $p = 0.07$) as the time interval between filtration surgery and development of endophthalmitis was significantly shorter in patients treated with antiproliferative agents ($p = 0.001$).

Conclusions—These results provide strong evidence of an increased risk of late endophthalmitis in patients who have diabetes mellitus or have had an episode of blebitis and suggest antiproliferative agents may also have an important role. (*Br J Ophthalmol* 2000;84:1349–1353)

Late endophthalmitis is an infrequent and potentially devastating complication of glaucoma filtering surgery. Not only may it occur in the unsuspecting patient many years after the procedure and progress with great rapidity, but the organisms responsible are often more virulent than those associated with post-cataract endophthalmitis.¹

In the era of full thickness filtration procedures the reported rate of late endophthalmitis was up to 9%² and this was noted to decrease

to 0.3%–1.5% following the introduction of partial thickness sclerostomies.^{3,4} The widespread introduction of antiproliferative agents such as 5-fluorouracil (5-FU) and mitomycin C (MMC) in the early 1990s, which result in thinner and less vascular filtering blebs,⁵ has led to concern that antiproliferatives may result in an epidemic of post-trabeculectomy endophthalmitis.⁶ Antiproliferative use certainly causes disordered conjunctival epithelial and stromal morphology,^{7,8} which is likely to reduce the filtering bleb's resistance to transconjunctival bacterial migration.³ However, the paucity of accurate incidence data for post-trabeculectomy endophthalmitis has hindered assessment of the risks of individual antiproliferatives.

While there is an increased risk of late endophthalmitis associated with inferiorly positioned trabeculectomies,^{9,10} the risk associated with antiproliferatives applied to the superior conjunctiva is less clear cut.^{10–12} For this reason a case-control study was undertaken to determine the relative importance of potential risk factors, particularly antiproliferatives, in the development of post-trabeculectomy endophthalmitis at this academic centre based practice.

Methods

CASES AND CONTROLS

Patients presenting with post-trabeculectomy endophthalmitis to Moorfields Eye Hospital over a 6½ year period (January 1993 to June 1999) were considered for inclusion. Patients treated during the period until December 1997 were identified retrospectively by cross referencing computerised records from the microbiological laboratory database with patients under the care of the glaucoma service clinics. (All cases of endophthalmitis have microbiological analysis and are included on this database.) In the subsequent 18 months (January 1998 to June 1999) cases were identified prospectively from those presenting to the glaucoma clinics. For each potential case the clinical records were reviewed to determine whether the treatment episode fulfilled the case definition for inclusion.

CASE DEFINITION

Late post-trabeculectomy endophthalmitis was diagnosed by the presence of vitreous inflammation together with a combination of bleb injection (or a bleb infiltrate) and anterior chamber inflammation (> 2+ of cells and flare) presenting 4 or more weeks after filtration surgery. Three control patients were chosen for

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Table 1 Relation between study factors and post-trabeculectomy endophthalmitis by case-control status

Study factor	Cases (n = 23)		Controls (n = 69)		Unadjusted odds ratio	95% CI	p Value*
	No	%	No	%			
Male	15	(65)	38	(55)	1.53	(0.57, 4.25)	0.47
Age > 60 years	11	(50)	40	(58)	0.73	(0.27, 1.94)	0.62
Right eye	14	(61)	38	(55)	1.30	(0.48, 3.44)	0.81
Phakic	19	(83)	62	(90)	0.54	(0.14, 2.31)	0.46
Fornix based flap	9	(39)	31	(45)	0.79	(0.29, 2.08)	0.81
Releasable sutures	14	(61)	45	(65)	0.83	(0.31, 2.28)	0.80
Diabetes mellitus	5	(22)	4	(6)	4.51	(1.02, 20.29)	0.04
Bleb leak	8	(35)	17	(25)	1.63	(0.65, 4.96)	0.42
Blebitis	6	(26)	2	(3)	11.82	(2.21, 88.31)	0.003
Intraoperative antiproliferative use	20	(87)	46	(67)	3.33	(0.95, 15.19)	0.07
5-Fluorouracil	9	(39)	17	(25)	1.97	(0.70, 5.37)	0.19
β Radiation	2	(9)	5	(7)	1.22	(0.15, 6.66)	1.00
0.1 Mitomycin	2	(9)	7	(10)	0.84	(0.11, 4.15)	1.00
0.2 Mitomycin	3	(13)	11	(16)	0.79	(0.16, 3.00)	1.00
0.4 Mitomycin	4	(17)	6	(9)	2.21	(0.50, 8.85)	0.26
Total mitomycin	9	(39)	24	(35)	1.21	(0.44, 3.21)	0.80
Postoperative subconjunctival 5-FU	5	(22)	10	(15)	1.64	(0.45, 5.40)	0.52

each endophthalmitis case by selecting from the operating theatre records the three patients undergoing trabeculectomy immediately following each index case. The study followed the tenets of the Declaration of Helsinki and was approved by the hospital's research ethics committee.

DATA COLLECTION

The data collected for each subject (summarised in Tables 1 and 2) included sex, age, diabetic status, and the nature of the filtration surgery (including technique employed, fornix/limbal based conjunctival flap and, where relevant, dose, duration, and type of antiproliferative agent application). The postoperative interventions (including bleb needling and postoperative subconjunctival 5-FU injections) and the clinical features of the inflammatory episode (including Seidel positivity, grading of anterior chamber cellular reaction, presence of hypopyon, demonstration of vitritis with ultrasonography, and visual acuity) were recorded together with the time interval between surgery and the development of endophthalmitis. The occurrence of episodes of blebitis, defined as bleb infection in the absence of clinically apparent vitreous involvement, and whether this was concurrent with or preceded the endophthalmitis, was also noted. The number of patients undergoing trabeculectomy each calendar year was established from the hospital's computerised record of surgical activity in order to estimate the proportion of trabeculectomy cases that presented to Moorfields with subsequent endophthalmitis.

MICROBIOLOGICAL PROTOCOL

Anterior chamber and/or vitreous samples (as noted in Table 2) were processed according to a standard protocol. Each sample was inoculated on to blood, R2A, and Sabouraud's dextrose agar as solid phase media with cooked meat, brain-heart infusion, and thioglycolate broth used as enrichment media. Conjunctival cultures were not collected since organisms isolated

from ocular surface swabs frequently differ from those cultured from intraocular samples.^{1 13}

STATISTICAL ANALYSIS

Matching was employed in this study as a convenient method of choosing controls rather than as a means to control bias or increase precision of the odds ratios explored. However, since in general the analysis should reflect the design, we conducted both matched and unmatched analyses using respectively conditional logistic and logistic regression.¹⁴ Results were very similar, therefore we have presented only the simpler to interpret unmatched results—as odds ratios together with exact mid p confidence intervals and the p value of the Fisher's exact test of association. We did not compute adjusted odds ratios owing to the comparatively small data set and because the results of the univariate analyses did not suggest confounding. Analyses were conducted using STATA CORP 97: Stata Statistical Software Release 5 (Stata Corporation, USA) and STATXACT version 2 (Cytel Software Corporation, Cambridge, MA, USA).

Results

Twenty six episodes of post-trabeculectomy endophthalmitis were identified (seven prospectively) of which three were excluded from analysis: two from patients who presented 5 and 14 days respectively following surgery and the other being the second occurrence of post-trabeculectomy endophthalmitis in the same patient. All cases had undergone glaucoma filtration surgery at Moorfields Eye Hospital. The characteristics of the 23 cases and 69 controls (Table 1) were similar with regard to a wide number of variables including age, sex, eye affected, phakic status and the surgical technique employed.

An episode of blebitis, which occurred in six of 23 cases (26%) and two of 69 controls (3%), was statistically significantly associated with post-trabeculectomy endophthalmitis; odds ratio 11.82 (95% CI 2.21–88.31), $p = 0.003$.

Table 2 Clinical and microbiological features from 23 patients with post-trabeculectomy endophthalmitis

Glaucoma type	Time interval	Date of presentation	Antiproliferative used	Preop IOP (mm Hg)	Preop medications	IOP at last follow up (mm Hg)	Medications at last follow up	Organism isolated	Decrease in acuity (Snellen lines)	Acuity at last follow up
POAG	6 years	1999	5-Fluorouracil	27	1	14	1	<i>Moraxella</i>	0	Sn 6/9
POAG	14 years	1999	None	24	2	22	3		2	Sn 6/18
POAG	4 years	1999 [¶]	5-Fluorouracil	28	3	9			1	PL
POAG	6 years	1999	None	35	4	10			1	Sn 6/12
POAG	1 month	1998	Mitomycin (0.2)	24	3	10		<i>S viridans</i>	6	CF
POAG	4 months	1998 [°]	5-Fluorouracil	25		12			4	Sn 6/24
Congenital	3 years	1998 ^{‡¶}	Mitomycin (0.4)	33	2	10		Gram -ve bacillus [†]	3	CF
AACG	7 months	1998 [¶]	5-Fluorouracil	22	3	12			3	Sn 6/36
POAG	15 months	1998 ^{‡¶}	5 Fluorouracil	26	1	4		<i>S pneumoniae</i>	5	HM
POAG	1 month	1998 ^{‡¶}	Mitomycin (0.1)	18	1	16	1	<i>S pfneumoniae</i>	9	PL
NTG	6 months	1998	Mitomycin (0.1)	16		12			3	Sn 6/24
POAG	1 month	1997 ^{‡§}	5-Fluorouracil	25	3	21	3	Gram -ve bacillus [†]	0	Sn 6/24
POAG	3 months	1997	5-Fluorouracil	24	2	12			0	Sn 6/9
POAG	1 month	1997	Mitomycin (0.2)	22	2	21	2		1	Sn 6/12
POAG	4 years	1997	Mitomycin (0.2)	22	3	3		*	0	HM
Congenital	9 years	1997	β radiation	30		20	1	<i>H influenzae</i>	1	HM
Traumatic	15 years	1996	None (bleb revision)	36		13			0	Sn 6/9
POAG	1 month	1996 [¶]	5-Fluorouracil	26	2	18	2	<i>S aureus</i>	0	Sn 6/9
POAG	2 years	1996 [¶]	Mitomycin (0.4)	24	3	10		<i>α hamolytic streptococcus</i>	8	PL
Congenital	4 months	1995 [‡]	Mitomycin (0.4)	34		16	4		1	CF
Congenital	4 years	1995 ^{‡°}	Mitomycin (0.4)	46	2	30	3	<i>S albus</i>	1	PL
POAG	1 month	1994 [‡]	5-Fluorouracil	26	2	18	2		0	Sn 6/9
Congenital	6 years	1993	β radiation	28	1	Phthisis			2	NPL

POAG = primary open angle glaucoma; Congenital = congenital glaucoma; AACG = acute angle closure glaucoma; NTG = normal tension glaucoma; Time interval = interval between filtration surgery and episode of post-trabeculectomy endophthalmitis in whole months or years; 1999 refers to the first 6 months of 1999; β radiation applied at a dosage of 750 cGy; Preoperative IOP = IOP before filtering surgery; *no vitreous tap performed (all other cases treated with intravitreal vancomycin (2 mg) and amikacin (0.4 mg); †demonstrated with light microscopy, no growth on culture media; ‡ultrasound confirmation of vitreous involvement; §denotes bleb needed postoperatively; °denotes previous episode of blebitis; ¶denotes bleb leak. All antiproliferative agents were applied for 5 minutes and the dose of mitomycin C is shown in parentheses. No patients were prescribed topical antibiotics for more than 3 weeks following trabeculectomy surgery.

The mean time interval between these treated episodes of blebitis and the subsequent development of endophthalmitis was 9 weeks (SD 4.2). Diabetes mellitus occurred more commonly in cases than controls (five of 23 (22%) versus four of 69 (6%)) and was also statistically significantly associated with post-trabeculectomy endophthalmitis; odds ratio 4.51 (95% CI 1.02–20.29), $p = 0.04$. Antiproliferatives were widely used intraoperatively with mitomycin C being applied most frequently in both cases and controls. The time interval between filtration surgery and development of endophthalmitis was significantly shorter in antiproliferative treated cases ($p = 0.001$, rank sum test). Use of an antiproliferative agent (20 of 23 cases (87%) versus 46 of 69 controls (67%)) was associated with subsequent endophthalmitis with an odds ratio of 3.33 (95% CI 0.95–15.19), although these results did not reach statistical significance, $p = 0.07$.

The clinical characteristics of the 23 patients diagnosed with post-trabeculectomy endophthalmitis and the organisms isolated in 10 cases (43%) are summarised in Table 2. The median time interval between glaucoma surgery and endophthalmitis was 15 months (range 1–180) and the mean reduction in acuity following the episode of endophthalmitis was two Snellen lines (SD 2.6). At the latest follow up (median 7 months, range 1–154) 10 of 23 eyes (43%) required medication to control the intraocular pressure and a further three eyes (13%) were either hypotonous or phthisical.

Discussion

Case-control methodology was applied to patients presenting with post-trabeculectomy

endophthalmitis to a single hospital over a 6½ year period in order to clarify the risk factors for developing the condition.

The results at the univariate level provide strong evidence that the odds of endophthalmitis are increased approximately 12-fold (OR 11.82, 95% CI 2.21–88.31, $p = 0.003$) in a patient in whom blebitis has occurred. This result is in keeping with the recognised ability of blebitis to progress to endophthalmitis¹⁵ and it is likely that the changes in bleb morphology that predispose to bleb related infection increase susceptibility for subsequent endophthalmitis. Although the confidence interval associated with the odds ratio is wide, illustrating the imprecise nature of this estimate, even the lower confidence limit lies well above unity. These data also provide evidence that endophthalmitis is more likely in a patient who has diabetes mellitus (OR 4.51, 95% CI 1.02–20.29, $p = 0.04$); a finding in keeping with diabetes being a proved risk factor for other types of endophthalmitis.^{16 17}

Although the power of this study was limited—a 57% chance of detecting an odds ratio of 5 (assuming $\alpha = 0.05$, three controls per case and 70% exposure among controls)—these data provide some evidence that the odds of endophthalmitis may be greater in patients in whom antiproliferatives are used ($p = 0.07$). A patient treated with antiproliferatives is estimated to be three times as likely to develop endophthalmitis as one who is not; however, the 95% confidence interval is just consistent with there being no difference in odds. An adjusted odds ratio was not computed because of the limited data set and because of concerns that blebitis may lie along a postulated causal

path between antiproliferative use and endophthalmitis. An association was also found between antiproliferative use and a shorter time interval to the development of endophthalmitis ($p = 0.001$). This result may, however, partly reflect ascertainment bias as the study included patients developing endophthalmitis within a 6½ year period (patients undergoing trabeculectomy in the era before widespread antiproliferative agent use could have developed endophthalmitis within a year or two of surgery without being ascertained). Other factors were not found to be associated with endophthalmitis.

These results indicate that blebitis, diabetes mellitus and, possibly, antiproliferative use are associated with subsequent endophthalmitis. Migration of bacteria across the filtering bleb is recognised to be the initial step in the development of blebitis^{3 18} and ordinarily such spread is prevented by the physical properties of the bleb together with the eye's innate immune response. Antiproliferative use alters the thickness, cellularity, and vascularity of the filtering bleb's conjunctiva. The thinner and relatively avascular blebs that result frequently have areas of absent conjunctival epithelium which are demonstrable both microscopically³ and clinically. These areas of denuded epithelium and the underlying full thickness stromal damage⁷ compromise the bleb's physical barrier function and affect the conjunctival contribution to the ocular innate immune response. One component of this response is a family of highly conserved cysteine rich antimicrobial peptides, called defensins, that combat infection at a wide range of mucosal surfaces.^{19 20} The constitutive conjunctival expression of certain defensin isoforms (β_1) at a high level²¹ suggests that they are important components of the conjunctiva's innate defences. β Defensin expression will be altered in unepithelialised areas of the filtering bleb and we hypothesise that the combination of breaches in the bleb's barrier function with altered conjunctival β defensin production may account for part of the observed increased susceptibility to infection of antiproliferative agent treated blebs.

Direct comparison between published reports of post-trabeculectomy endophthalmitis cases is hampered by variation between studies regarding factors including study design, case definition, case mix, antiproliferative agent use (both type, dose and duration of administration), as well as the nature and site of surgery (superior/inferior filtration) and the treatment received on presentation with endophthalmitis.^{1 9-11 15 22-25} For these reasons we have limited comparison of the clinical features (Table 2) of this group of patients to noting that the visual outcome and rate of filtering bleb survival are broadly comparable with previous reports (and in a study period partially predating the Endophthalmitis Vitrectomy Study²⁶ that 22 of the 23 cases received intravitreal antibiotics). The poor prognosis associated with post-trabeculectomy endophthalmitis is best highlighted by the fact that just three of 23 eyes achieved satisfactory intraocular pressures without treatment and a Snellen acuity greater than 6/24. Overall epi-

sodes of post-trabeculectomy endophthalmitis were associated with a high likelihood of trabeculectomy failure (57%) and a mean reduction in acuity of two Snellen lines. This measurement understates the effect of visual loss in individual patients with poor initial acuity as a result of advanced or congenital glaucoma and the number of patients in the latter subgroup (five of 23) may skew the overall visual results reported. The proportion of cases (52%) occurring more than 1 year postoperatively with some occurring several years later indicates that the risk of post-trabeculectomy endophthalmitis is long lasting, perhaps for at least the lifetime of a functioning bleb.⁶ This is of particular concern in younger glaucoma patients in whom surgery is the main treatment modality. The design of the study precluded calculation of incidence data owing to the likelihood of ascertainment bias and the study may have been biased to detecting fewer cases of late endophthalmitis than if all trabeculectomy cases had been followed prospectively. None the less the rise in the number of cases presenting to Moorfields is compatible with reports^{6 10 11} suggesting that the frequency of post-trabeculectomy endophthalmitis is increasing. Whether the more favourable bleb morphology achieved with larger areas of antiproliferative treatment²⁷ has the potential for reducing the frequency of this complication remains to be determined.

Proprietary interest: None

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