Risk factors for bleb related infection following trabeculectomy surgery: Ocular surface findings

A case-control study

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Synopsis

A case- control study investigating risk factors for bleb related infection following trabeculectomy. Chronic blepharitis was identified as the major risk factor (multivariate analysis OR 16.3 p=0.016).

Abstract

Purpose
Bleb-related infection is a devastating complication of trabeculectomy surgery. The aim of this study was to identify ocular risk factors for bleb related infection with specific emphasis on ocular surface parameters. It has been suggested that the frequency has increased since the introduction of antimetabolites, particularly mitomycin C.

Design:
A case control study

Method:

A clinical study of bleb related infection following trabeculectomy surgery to investigate risk factors by documenting historical data review from patients records, self reported questionnaire specific to ocular surface symptoms and a repeat detailed clinical examination of the lid, ocular surface and tear film.

Results:
28 cases and 31 controls were assessed. The overwhelming risk factor for development of bleb related infection was chronic blepharitis (multivariate analysis OR 16.3 (1.687-157.44) p=0.016). No increased risk was identified with antimetabolite used during trabeculectomy surgery (p=0.38) or the type of conjunctival reflection adopted for surgery (p=0.38). Neither age (p=0.32) nor dry eyes (p=0.13) were identified as risk factors.

Conclusion:

An increased risk of bleb related infection was identified in eyes with chronic blepharitis. To minimize the risk of infection following trabeculectomy surgery, it may be advisable to manage the lid disease in these patients prior to performing trabeculectomy surgery or offer an alternative treatment such as a shunt.

Introduction

Bleb Related Infection (BRI) following trabeculectomy is a serious complication resulting in severe visual loss[1]. BRI has been reported with both full thickness[2] and guarded sclerostomies[3]. Inferior bleb placement has such a high risk of BRI[4] that practice has changed to predominantly superiorly placed blebs. Other risk factors have been proposed including avascular blebs[5-7] bleb leak[8 9], blepharitis[10], 5 fluorouracil[11], mitomycin C[2 12], limbus based conjunctival flap[13], young age[4], diabetes[12], multiple filtration procedures[9] and bleb manipulation[14].
The cumulative incidence of BRI is fortunately rare, in the region of 1%[5 15]. With such a rare outcome the literature consists mostly of case series with few previous formal studies. This study was designed to specifically identify risk factors for BRI including those related to ocular surface disease.

Methods

Study Design
A case control study was undertaken of all patients undergoing trabeculectomy surgery at one tertiary referral centre between 1993 and 2002.

Approval was granted by the local Research Ethics Committee at Moorfields Eye Hospital. An attempt was made to contact and re-examine all patients who suffered an episode of BRI (cases) and a random sample of patients without BRI (controls) who also underwent trabeculectomy during that period.

A sample size of 26 subjects in each group would show an odds ratio of 6 with 95% confidence and 80% power in each group (Fleiss).

The index eye was the infected eye of the case. The control eye was a trabeculectomy randomly selected from the cohort of patients operated between the time periods between 1993- 2002. The contralateral eyes of all patients were also examined as the non- index eye. Thus data was collected on both index and non-index eyes. Due to logistic and practical reasons cases and controls were not masked.

Cases
All confirmed patients with blebitis or endophthalmitis following trabeculectomy at Moorfields Eye Hospital during the period of 1993- 2002 were identified. Case ascertainment was maximized by cross reference of admission records in accident and emergency, operating theatres, pathology department, medical records and the infection control department. BRI was confirmed by medical record examination. BRI was

graded as blebitis and bleb related endophthalamitis (when vitreous was involved).

Cases who had trabeculectomy surgery outside Moorfields Eye Hospital were excluded from the study. When the enrolled eye had more than one episode of BRI the first episode was used as the index episode for inclusion in the study.

Controls
Controls were randomly selected from the 4886 patients who underwent trabeculectomy during the period 1993- 2002. If two trabeculectomies were performed in the same patient during that period, the first trabeculectomy was used as the index eye. Two controls per BRI case were selected.

Data collection
Demographic information, detailed ocular history, type of BRI (blebitis or endophthalmitis), systemic history and surgical details were collected. An effort was made to invite every case and control to participate in the study. Those still in attendance at the hospital were contacted directly, those who had been discharged or for whom there was no current appointment were contacted through their general practitioners. Each participant was invited to the clinic by mail.

At the study visit, patients were given an information leaflet. If willing to participate, written consent was taken. Historical data were collected from patient records including demographic information, past medical history, past ocular history including surgery, and details of the index surgery including subsequent management.

Participants completed a self-administered questionnaire especially designed to investigate ocular surface symptoms. Participants then underwent a clinical examination of both eyes. The clinical examination was validated by pilot studies prior to the data collection ensuring repeatable and reproducible assessment of all key signs including acute and chronic blepharitis, ptosis, lagophthalmos, bleb morphology, staining pattern of the conjunctiva and cornea. Non-invasive tests were performed prior to invasive tests in order to avoid interference with the ocular surface. The validation and consistency data was analyzed with Bland Altman and Kappa analysis to draw agreement between two independent examiners. (Appendix 1) It was not practical to mask the examiner to case or control status.

Appendix 2 and 3 contains the data collection forms and manuals for all aspects of the study. Detail is given below concerning the assessment of blepharitis.

Ocular surface definitions
Blepharitis is broadly classified as anterior and posterior blepharitis based on the anatomy of the lid margin and its involvement. Figure 1 illustrates

the classification we used for blepharitis. This was largely derived from the work of MacCulley et al, Bron AJ et al and Yanoff et al[16-18] and proved reproducible.

Data was entered on bespoke data entry forms and transferred to electronic records using epidata 3.1. Double data entry with cross checking was used and data cleaning undertaken to maximize data integrity prior to analysis.

Data analysis

Analysis was undertaken using iStata version 7.0 (http://www.stata.com/) Contingency tables were constructed before univariate logistic regression for individual potential risk factors. Finally multivariate logistic regression was utilized to investigate confounding factors. A model was constructed that included all risk factors identified in univariate analyses and also those suggested as important in previous studies.

Results

Between 1993 and 2002, 70 cases of BRI were identified in 70 patients. From the list of all 4886 trabeculectomies during the same period, 140 controls were identified.

Twenty-eight cases (40%) were successfully recruited for clinical examination. Of the 42 BRI cases not assessed, 9 died, 1 was bedridden, 2 declined, 2 had undergone recent eye surgery, 1 could not be assessed as the eye was phthisical, 1 did not have records, 1 had moved overseas, 6 did not respond to the invitation to the study and 19 were not contactable and were not attending clinic at the time of recruitment. Of the 19 patients who were not attending the hospital 14 patients were above the age of 75 years with equal number of male and females. Four patients were between the ages of 50 -75 years and all were males. Only one patient was less than 50 years and she had moved abroad.

Thirty-one controls (22%) were recruited for clinical examination. Of the 109 not assessed 20 died, 1 was unwell, 2 declined as recent eye surgery, 5 were children and were excluded, 10 did not respond to invitation and 71 were not contactable. Of those who were not contactable, 36 were male and 35 female. Ten patients had moved outside London. Of the 61 who did not have follow-up in clinic with addresses around Greater London there were 30 male and 31 females. Of these 61 patients, 36 patients were over 75 years of age (male 14, female 22), 16 between 50- 74 years (male 10, female 6), 4 between 30-50 years (male 2, female 2) and 5 between 17-29 years (male 4, female 1).

Table 1: Demographics of cases and controls included in study of risk factors for bleb related infection

	Cases (%)	Controls (%)	Fisher exact
Gender			
Male	18 (64%)	23 (74%)	0.7 p=0.4
Ethnicity			
Caucasian	14 (50%)	22 (71%)	7.2 p=0.03
Asian	3 (11%)	6 (19%)	
African or Caribbean	11 (39%)	3 (10%)	
Age			
15-34	2 (7%)	1(3%)	1.0 p=0.8
35-54	2(7%)	3(10%)	
55-74	13(46%)	12(39%)	
75-94	11(39%)	15(48%)	
Systemic history			
Diabetes	9 (22%)	6 (19%)	1.3 p=0.3
Asthma	1 (4%)	3 (10%)	0.9 p=0.4
Rheumatoid	1 (4%)	1 (3%)	0.01 p=0.9
Thyroid	3 (11%)	2 (6%)	0.3 p=0.6
Eczema	3 (11%)	0 (0%)	3.4 p=0.06
Hypertension	19 (68%)	16 (52%)	1.6 p=0.2
Hypercholesterolemia	11 (39%)	9 (31%)	0.4 p=0.5
Ocular history			
None	10 (36%)	14 (45%	4.3 p=0.5
Dry eyes	3 (11%)	1 (3%)	1.3 p=0.3
Lid abnormality	2 (7%)	1 (3%)	0.5 p=0.5
Uveitis	2 (7%)	3 (10%)	0.1 p=0.7

Corneal disease	5 (18%)	2 (6%)	1.8 p=0.2
Cataract	6 (21%)	10 (32%)	0.8 p=0.4
Allergy to drops	7 (25%)	3 (10%)	2.4 p=0.1
Diagnosis			
POAG*	20 (71%)	18 (58%)	2.0 p=0.6
PACG*	1 (4%)	4 (13%)	
NTG*	1 (4%)	1 (3%)	
Secondary*	6 (21%)	8 (26%)	
Number of glaucoma drops at time of last examination			
0	9 (32%)	10 (32%)	0.1 p=1.0
1	5 (18%)	6 (19%)	
2	7 (25%)	7 (23%)	
3	5 (18%)	6 (19%)	
4	2 (7%)	2 (6%)	

*POAG- primary open angle glaucoma, PACG- primary angle closure glaucoma, NTG - normal tension glaucoma, secondary -secondary glaucoma

One case of BRI was of Chinese ethnicity, for the purposes of analysis we included this case in the group of Caucasians. There were more Caucasians in the control group and more African and Caribbean patients in the case group (deleted 71% Caucasians and 39% African and Carribbean) (p=0.03). Three cases of BRI had a history of eczema and none of the controls (deleted 11% in cases p=0.06). There were slightly more cases of primary open angle glaucoma (POAG) in the cases and more of primary angle closure glaucoma (PACG) in the controls (POAG 71% p=0.6). There was no difference between groups in the number of drops being taken to the index eye at last examination. Table 1.

Table 2: Surgical details of trabeculectomy surgery included in the analysis of risk factors for bleb related infection

	Cases (%)	Controls (%)	Fisher exact
Number previous trabeculectomies			
1	20 (71%)	24 (77%)	0.3 p=0.9
2	6 (21%)	5 (16%)	
3	2 (7%)	2 (6%)	
Antimetabolite used at last surgery			
None*	1 (4%)	5 (17%)	3.7 p=0.2
5 FU + one beta (control)*	9 (39%)	15 (50%)	
MMC*	13 (57%)	10 (33%)	
Limbus/fornix based flap (4 not recorded 1 control and 3 cases)			
Limbus**	17 (68%)	14 (47%)	2.5 p=0.1
Fornix**	8 (32%)	16 (53%)	

*None – No antimetabolite use 5FU – 5 Flurouracil, Beta- Beta radiation, MMC- Mitomycin C
**Limbus- limbus- based conjunctival flap reflection, Fornix- fornix- based conjunctival flap reflected

No major difference was seen between the groups for any surgical parameter (Table 2). Slightly more cases had received mitomycin C and had a limbus based conjunctival flap at the time of their last trabeculectomy.

The questionnaire of ocular symptoms showed no difference between cases and controls for any symptoms relating to dry eyes or ocular discomfort.

Table 3: Parameters of ocular surface examination included in the analysis of risk factors for bleb related infection

Acute blepharitis lids	**Cases (%)**	**Controls (%)**	**Fischer exact**
No	6 (21%)	14 (45%)	3.7 p=0.054
Yes	22 (79%)	17 (55%)	
Chronic blepharitis lids			
No	13 (46%)	30 (97%)	18.9 p<0.001
Yes	15 (54%)	1 (3%)	
Schirmer test			
1-4mm	7 (25%)	7 (23%)	6.0 p=0.2
5-9mm	10 (36%)	11 (35%)	
10-14mm	3 (11%)	9 (29%)	
15-19mm	5 (18%)	4 (13%)	
20+mm	3 (11%)	0 (0%)	
Tear film breakup time (secs)			
1-4	8 (30%)	4 (13%)	9.8 p=0.043
5-9	8 (30%)	8 (26%)	
10-14	2 (7%)	13 (42%)	Chi^2 trend
15-19	7 (26%)	5 (16%)	9.5 p=0.02
20+	2 (7%)	1 (3%)	
Fluorescein stain of bleb			

Yes	14 (52%)	17 (55%)	0.1 p=0.8
Rose Bengal stain of bleb			
Yes	3 (11%)	3 (10%)	0.02 p=0.9
Superficial punctate keratitis			
Yes	9 (32%)	14 (45%)	1.0 p=0.3
Ferning			
1	4 (14.29%)	8 (25.81%)	4.0257 p=0.4
2	6(21.43%)	6 (19.35%)	
3	14 (50%)	15 (48.39%)	
4	0 (0%)	1 (3.23%)	
5	4 (14.29%)	1 (3.23%)	
Palpebral aperture width			
1-5	3 (11%)	1 (3%)	4.3 p=0.12
6- 9	16 (59%)	13 (42%)	
10+	8 (30%)	17 (55%)	
Bleb leak			
Yes	4 (14%)	2 (6%)	1.0 p=0.3

It can be seen the tear film break up time was shorter in a greater proportion of cases. This related to an increased proportion blepharitis - predominantly chronic blepharitis. A majority of blepharitis was mild, only 6 individuals (4 cases) had moderate or severe acute blepharitis and 2 individuals (1 case) moderate chronic blepharitis with no severe chronic blepharitis. No other ocular parameter showed a major difference. There was one eye (control) with loss of corneal sensation and two eyes (both cases) had proud sutures. Four eyes in the cases had bleb leaks compared to two controls. Blebs were present in approximately three quarters of both cases and controls (75% cases and 81% controls (p-=0.6). Table 3.

Table 4: Risk factor analysis in case control study investigating bleb related infection

Risk factor	Univariate OR (95% CI)	P value	Multivariate OR (95%CI)	P value
Gender male	1.597 (0.523-4.874)	p= 0.41	0.571 (0.802-4.059)	p= 0.575
Age	0.991 (0.956-1.027)	p= 0.62	0.962 (0.892-1.037722)	p = 0.317
Ethnicity	1.433 (0.749-2.744)	p= 0.28	2.175 (0.542-8.723)	p= 0.27
Allergy to drops	3.111 (0.718-13.48)	p= 0.13		
History dry eyes	1.282 (0.811-2.027)	p= 0.13		
Antimetabolite used at last surgery	2.361 (0.960-5.806)	p= 0.061	0.324 (0.0261-4.032)	p= 0.381
Limbus vs fornix based flap	0.412 (0.136-1.243)	p= 0.12	0.725 (0.121-4.351)	p= 0.381
Subsequent cataract surgery	2.252 (0.780-6.505)	p= 0.13	1.769 (0.319-9.790)	p= 0.513
Ferning	1.411(0.863-2.306)	p= 0.16	1.305 (0.565-3.013)	p= 0.532
Acute blepharitis	3.020 (0.959-9.506)	p= 0.059	0.660 (0.1512.888)	p= 0.582
Chronic blepharitis	34.62 (4.129-290.20)	p= 0.001	16.300 (1.687-157.44)	p= 0.016
Palpebral aperture	0.388 (0.154-0.976)	p= 0.044	0.648 (0.154-2.729)	p= 0.555
Tear Break up time	1.28 (0.807-2.015)	p= 0.30	0.554 (0.136-2.969)	p= 0.491
Leak	1.26 (0.807-2.015)	p= 0.30		

In univariate analysis the results reflect the contingency tables. Candidates included in the multivariate modeling were use of MMC at the last surgery, limbus based conjunctival flap, cataract surgery following the last trabeculectomy, poor ferning, acute blepharitis, chronic blepharitis, a wide palpebral aperture and a reduced tear film break-up time. Table 4. The model demonstrated chronic blepharitis as the dominant risk factor. Only 6 leaks were identified in the study population, (4 in case eyes and 2 in control eyes) and in univariate analysis this was not significant and addition of bleb leak to the multivariate analysis was non-contributory. Acute blepharitis was covariant with chronic blepharitis.

Discussion

The striking finding from this study is the association of chronic blepharitis with BRI. This finding could, of course, be due to selection bias. We were only able to recruit 28/70 cases and 31/140 controls to the study. For a majority this was due to inability to contact eligible participants. It seems unlikely that cases with chronic blepharitis would be preferentially contactable and those controls with chronic blepharitis preferentially non-contactable. A slightly higher number of males were lost to follow-up among the cases compared to the controls. The effect size of chronic blepharitis is so great we believe this makes the possibility of no risk from posterior blepharitis unlikely. Another source of potential bias is the inability to mask the observer to the outcome since many eyes with endophthalmitis bear recognizable sequelae on examination.

A few studies have previously suggested the association of blepharitis with BRI. Although this study is not the first one to report blepharitis as a risk factor for BRI but the first one to report it in detail. Radhakrishnan et al reported in a retrospective review of 23 patients with culture positive blebitis cases. Whilst their main finding was cystic avascular blebs in 91% cases they also reported there were 3 cases with blepharitis (17%)[12]. Jampel et al found blepharitis a risk factor for BRI in their univariate analysis RR 1.92 (95% CI 1.17- 3.14 p =0.009), however they did not report it in the multivariate analysis[2]. In this report Jampel et al recorded blepharitis from documentation in the patient's records whereas our study examined each patient thereby improving case ascertainment. A recent study by Kim et al however did find chronic blepharitis to be a significant risk factor for BRI (HR 7.6 p=0.003)[19]. This study was of a similar size to ours but relied on medical notes for the clinical findings thus was prone to recording bias.

In the majority we found mild chronic blepharitis. Although our clinical examination was performed a long time after the BRI event it is likely that, unlike acute blepharitis which might receive treatment at the time of diagnosis, chronic blepharitis would persist for years. In our study acute blepharitis was a risk factor in univariate analysis and was identified at the time of examination but was not a risk factor in the multivariate analysis as a result of covariance. The chronic blepharitis was present in both eyes of all cases.

Why chronic blepharitis should be associated with BRI is unclear. Seal et al reported 88% of patients with chronic non- ulcerative blepharitis and meibomianitis showed high levels of tear lysozyme, ceruloplasmin, IgG and IgA when cultures of the lid and conjunctiva were obtained. It was suggested that these lid conditions had an inflammatory aetiology[20]. The reduced immunity from altered tear enzymes may reduce the defense mechanisms of the ocular surface and increase the colonisation of bacteria on the lid margin and result in infection in compromised eyes[21].

It could be that the chronic blepharitis may be a result of longstanding alteration in the ocular surface from chronic use of antiglaucoma eye drops. Jampel et al, however, found use of topical medication protective against BRI with RR 0.48 (95% CI 0.31- 0.73 p<0.001) which argues against this hypothesis[2].

There is a recognized association between blepharitis and dry eyes. Mathers et al recognized as early as 1993 that patients with meibomian gland drop out and low tear production by Schirmer test, had an increased risk of dry eye developing through evaporation[22]. Kim et al found with use of punctual plugs a risk factor for BRI (HR 6.1 p=0.022)[19]. The existence of dry eye signs however was not a risk factor for BRI in our study although any historical information will of course be subject to significant potential recall bias. There was no association between acute or chronic blepharitis and symptoms of dry eyes in our data. In addition there was no difference in tear production between the two groups as tested by Schirmer test. Although this test is not completely reliable[23 24] this does suggest an abnormality in the lipid layer may be the principal problem. The fact our cases tended to have a short tear film break up time supports this theory.

Many studies have attributed bleb leak as a risk factor for BRI[7,19]. Jampel et al also reported an association between bleb leak and BRI in their case control study but this was not present in multivariate analysis suggesting confounding[2]. In our study there were few bleb leaks (4 cases (14%) and 2 controls (6%)). These small numbers limit the ability of our study to detect anything but a very large effect. Many cases may have either had a leak repaired or spontaneously closed over the period following the BRI that might attribute to bleb failure in 25% of the cases. We have previously shown how difficult validation of bleb leakage is in a clinical situation[25] thus historical data will be prone to major bias. If there is a clinical event such as BRI the clinician is much more assiduous in looking for a leak. Bleb morphology has also been implicated. In our study a bleb was assessable and present in 19/27 (70%) controls and 16/24 (67%) cases (p=0.8). No major difference in morphology was seen with the exception of ischaemia which was seen in 3/26 (12%) controls and 7/22 (32%) cases (p=0.09). This is despite a likely change in morphology as a result of infection and/or treatment. The use of historical records for bleb morphology is extremely prone to unquantified bias as outlined by Kim et al.[19]

Lehmann reported an association between MMC and development of BRI[12] however both Jampel et al and our study did not find this association. Jampel et al excluded variables from the model that might be covariant with the use of MMC (such as previous intraocular surgery, presence of bleb leak, episodic or continuous use of antibiotic postoperatively). Following this MMC became a risk factor for BRI (RR 2.48; 95% CI, 1.06-5.83). The covariance may therefore be masking a true effect. None-the-less the effect size is still small relative to the effect size shown for blepharitis. Fewer numbers in our study would limit the ability to detect small effects.

An earlier reported historical comparison study in our Hospital suggested limbus (as opposed to fornix) based conjunctival dissection in trabeculectomies might be as a risk factor for BRI[13]. The current case control study does not show flap type as a risk factor. Again the small sample size limits our ability to show minor risk factors.

The findings of this study strongly indicate that an assessment for chronic blepharitis should be included in the pre-operative examination of patients in order to inform them and the surgeon of the risk of BRI with trabeculectomy surgery. The presence of significant chronic blepharitis is a direct contraindication to this form of surgery.

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As per ICMJE guidelines all the authors agree to be accountable for all aspects of the work done on this study. In addition each individual author's **contributions are-**
P Rai- Study design, validation, recruitment of study patients, clinical examination, data collection, data analysis, manuscript preparation and manuscript approval.
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Figure caption

Figure 1. Images and grading of acute and chronic blepharitis in case control study for bleb-related infection

Table Caption

Table 1. Demographics of cases and controls included in study of risk factors for bleb related infection.

Table 2. Surgical details of trabeculectomy surgery included in the analysis of risk factors for bleb related infection.

Table 3. Parameters of ocular surface examination included in the analysis of risk factors for bleb related infection.

Table 4. Risk analysis in case control study investigating bleb related infection