INFECTIVE ENDOPHTHALMITIS FOLLOWING VITREORETINAL SURGERY

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SUMMARY

Eleven cases of endophthalmitis occurring after vitreoretinal surgery are described. At Moorfields Hospital, London, from 1986 to 1990 the incidence of endophthalmitis after explant surgery with or without drain was 0.19% and after vitrectomy was 0.15%. We conclude that the parity may be due to the intraocular instrumentation of most conventional retinal detachment repair procedures. The best indicator of poor prognosis was speed of onset of symptoms, those with rapid evolution having the worst outcome; 2 of these cases were enucleated. Those presenting at 2–3 days had the best outcome, consistent with infection due to a less virulent organism. Delays in diagnosis were in part due to the posterior location of signs of infection. Potential risk factors amenable to prophylactic strategy were identified in 10 of the 11 patients. Supplementary prophylaxis using ciprofloxacin or imipenem is proposed for cases with an identifiable risk factor. After systemic administration these antibiotics achieve vitreous levels that exceed the MIC_{90} of the commonest causative pathogens.

There have been several reports of infective endophthalmitis after scleral buckling procedures[1–4] and after vitrectomy,[5–8] but the published rates for endophthalmitis after such surgery are low. Ho and McMeel found 2 cases out of 10 000 external retinal detachment repairs[1] (a rate of 0.02%) and Blankenship reported 3 in a series of 1500 vitrectomies[5] (rate of 0.2%). These figures fall at the lower end of the wide spread of reported endophthalmitis rates after cataract surgery, which range from 0.02% to 3%.[9]

The risk factors for the development of intraocular infection after an extraocular procedure should be very few, but vitrectomy may also be a safe procedure in this regard. During vitrectomy pathogens are denied easy access to the vitreous cavity via the scleral incisions by positive pressure which causes continuous net outflow of fluid. Furthermore the very process of vitrectomy removes a potential gel culture medium and tamponading agents such as silicone oil reduce to a minimum the remaining vitreous volume.

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Conventional repair now commonly involves an intraocular component; external drainage of subretinal fluid and the injection of gas are used in the D-ACE (Drain, Air, Cryotherapy, Explant) procedure[10] and inadvertent drainage of subretinal fluid may occasionally occur during buckle suturing. Ho and Tolentino described a septic choroidal effusion after buckling surgery in which the port of entry of infection was assumed to be the drainage sclerotomy.[11]

The changing preference of vitreoretinal surgeons for primary vitrectomy in managing difficult rhegmatogenous retinal detachments with large or posterior tears[12] means that there has been an increase in the number of these procedures performed in the last few years at the expense of explant surgery. The different rates of development of endophthalmitis associated with these procedures in the previously reported series above[1,5] might be expected to indicate that this trend would lead to more cases of endophthalmitis. The first aim of this study was to establish the rates of development of endophthalmitis in recent retinal surgical cases at Moorfields Eye Hospital, London. The second was to identify risk factors which might be either avoidable or amenable to prophylaxis.

PATIENTS, METHODS AND PROCEDURES

All cases of endophthalmitis diagnosed between 1 January 1986 and 31 December 1990 at Moorfields Eye Hospital were gathered for medical audit. The sources of cases were: standard forms issued by the Department of Pathology and completed on all cases of endophthalmitis admitted to the hospital, the microbiology laboratory records and the administrative records from the Hospital Activities Analysis (HAA) office. Patients who had developed endophthalmitis after vitreoretinal procedures performed between 1 January 1986 and 31 December 1990 were analysed retrospectively (Table I; procedures listed in chronological order).

The diagnosis of endophthalmitis was made on clinical

Table I.

Patient no.	Pre-op VA	State of retina	Afferent defect	Procedure	Time to onset	Presenting features	Symptoms to Rx
1	CF	Mac. off	N	D-ACE	3 days	Pain, hypopyon	Hours
2	6/9	Mac. on	N	D-ACE	3 months	Suppurative keratitis	5 days
3	6/18	Mac. on	N	Vit. oil explant	3 days	Poor view, cells + hypopyon at 2/7	Hours
4	6/9	Mac. on	N	Buckle	2 days	Poor view, cells + pain and pus at 2/7	1 day
5	PL	Mac. scar	Y	Vit. memb. peel	Hours	Pain, hypopyon, glaucoma	Hours
6	HM	Mac. off	N	D-ACE	Hours	Hypopyon, glaucoma	Hours
7	CF	Mac. off	Y	D-ACE	Hours	Glaucoma, unwell, fibrin at 2/7	2 days
8	HM	Mac. off	Y	Vit. oil	12 days	Pain, glaucoma, fibrinous uveitis	Hours
9	HM	Mac. hole	N	Vit. oil	Hours	Hypopyon, pain, hyphaema	Hours
10	CF	Total RD	Y	Vit. explant	4 months	Hypopyon, pain, glaucoma	7 days
11	PL	CRVO, diabetic	Y	Vit. gas	Hours	No view, hyphaema, hypopyon at 2/7	2 days

CRVO central retinal vein occlusion; Vit., vitrectomy; Single ch., single chamber/aphakic; cef, any cephalosporin; memb., PVR membrane; vanc, vancomycin; [a]Therapeutic vitrectomy.

grounds in 11 patients and confirmed on microscopy and/or culture in 7 of these. Four cases were included on clinical grounds alone: patient 2 had fibrinous uveitis after a D-ACE procedure, developed a hypopyon and suppurative keratitis at 3 months and was found to have an abscess at the site of a choroidal haemorrhage; patient 3 experienced pain and reduced acuity 3 days after vitrectomy and silicone oil injection which worsened on increased topical steroid, and a hypopyon developed on the fifth day; patient 9 developed a layered hypopyon and hyphaema with excessive pain within hours of a vitrectomy and oil injection and had numerous neutrophils in a specimen of aqueous fluid; patient 10 had endophthalmitis with delayed onset, but developed a hypopyon and excessive pain 4 months after a vitrectomy in spite of increasing doses of topical steroid, the resulting vitreous debris being sufficiently dense to require a therapeutic vitrectomy.

In order to calculate the rates of endophthalmitis, the total numbers of cases in which either vitrectomy or conventional procedures were performed during the same period were obtained from the records of the Hospital Management Information Department. It was not possible from information collated by the management information service to determine how many non-vitrectomy cases involved drainage of subretinal fluid or injection of a tamponading agent.

RESULTS

Incidence

The overall rate of endophthalmitis after vitreoretinal surgery based on the calculation of 6500 cases over 5 years was 0.17% (n = 11). For external procedures including D-ACE (2600 cases) the rate was 0.19% (n = 5). For vitrectomy (3900 cases) the rate was 0.15% (n = 6).

Presentation

The presenting signs of infection were anterior in 7 patients (Table I). Signs such as hypopyon were recognised immediately; there were, however, several patients (nos. 3, 4, 7 and 11) in whom the signs were initially confined to the posterior segment and their significance was not appreciated immediately. Pain supported the diagnosis in all 11 patients and was particularly severe in 6 (Table I), although it did not predate other diagnostic symptoms and signs.

Microbiological Specimens

An anterior chamber tap only had been done in 1 case (Table I: samples), vitreous tap or biopsy only in 2 and both aqueous and vitreous had been taken separately in 2. 'Single chamber' tap had been done in 4 aphakic eyes, the absence of the lens and its capsule simplifying the taking of anterior and posterior (aqueous or vitreous) fluid samples. Investigation had included Gram stain, aerobic and 5–10% CO_2-incubated blood agar cultures and cultures using Sabouraud's agar, Robertson's cooked meat broth, thioglycollate broth, nutrient broth and brain-heart-infusion broth. There was a positive microbiological yield from 3 of 4 vitreous taps, 2 of 4 single chamber taps and 1 of 3 aqueous taps.

Treatment

The management strategy for post-operative endophthalmitis did not follow a protocol; treatment depended chiefly on the severity of the signs. A therapeutic vitrectomy was done at the time of diagnostic tap in 1 case only (patient 10).

Antibiotics were given intravitreally to 5 patients, intravenously to 7 and orally to 1 (Table I). Ward-administered subconjunctival antibiotics were given in 2 cases only. Intensive topical antibiotics were given to all but 1 patient; 9 received two antibiotics, 1 patient received intensive methicillin only, and 1 received 6-hourly chloramphenicol drops.

Systemic steroid was given to 3 patients immediately in 1 case (patient 5) with proven *Proteus* infection, after 5 days in another with alpha-*Streptococcus* infection (patient 7) and after 9 days in a culture-negative patient who was not improving (patient 1). Intensive topical steroid was given to 9 patients and this predated the diagnosis of endophthalmitis in 2 cases (patients 2 and 10). One further patient received topical steroid four times a day.

Risk Factors

Ten of the 11 cases were associated with a risk factor

Sample	Result	Intravitreal antibiotic	Systemic antibiotic	Oral prednisolone	Cause of poor outcome	Final VA
Aq. tap Vit. tap	Neg. *S. epid.*	cef + gent	ciprofloxacin	Yes	–	
Corneal scrape	Neg.	–	cef magnapen	–	suprachoroidal abscess delay in diagnosis	NPL
Single ch. tap	Neg.	–	flucloxacillin	–	–	6/6
Explant	*S. aureus*	–	cef + gent fucidin	–	–	6/9
Vit. tap	*Proteus*	cef + gent	gent ticarcillin	Yes	*Proteus* infection	Evis.
Single ch. tap	G+ ve cocci(–)	cef + gent	–	–	original condition macula off, glaucoma	PL
Single ch. tap	alpha *Strep.*	cef + gent	cef + gent	Yes	original condition, macula off, PVR	HM
Aq. tap	S. *epid.*	–	cef	–	original condition macula off, PVR	HM
Aq. and vit. tap	Neg	–	–	–	original macular hole (relatively good outcome)	6/60
Single ch. tap[a]	Neg	–	–	–	original condition, delay macula off, glaucoma	PL
Vit. tap	G+ve cocci(-)	amik + vanc	ciprofloxacin	–	devastating infection in diabetic	Evis.

amik, amikacin; gent, gentamicin; Mac., macula; Aq., aqueous; Vit., vitreous; RD, retinal detachment; PVR, proliferative vitreoretinopathy; Evis., evisceration.

(Table II), the commonest being a long operation. Procedures of 2 hours or more were considered potential risk factors (see Discussion) for intraocular infection in 6 cases. Thus 8 of the 11 patients had two or more risk factors.

Possible medical risk factors identified in 5 patients were diabetes, sickle-cell disease, active diverticulitis and a recent quinsy. Five had undergone previous intraocular surgery (Table II). Per-operative complications occurred in 2 patients; lens touch in 1 was probably irrelevant but an annular choroidal haemorrhage in another was the site of abscess formation.

Pre-operative antibiotic drops had been omitted in 5 cases and in another 2 there had been no record of any subconjunctival antibiotic given at the end of detachment surgery (subconjunctival gentamicin or ceftazidime had been used in the others).

Outcome

Three patients achieved an acuity of 6/9 or better. In the remaining patients the final acuity was 6/60 or worse. In 5 the initial retinal pathology contributed significantly to the poor final acuity; no patient who had a relative afferent defect at presentation had a useful visual outcome (see Table I).

The outcome for eyes which required vitrectomy was particularly poor (Table I); 2 were enucleated. The 3 in whom silicone oil tamponade had been employed fared better than the others, 1 showing no change from the pre-operative acuity (patient 8) and the other 2 an improvement (patients 3 and 9).

The mean number of days in hospital was 9.4 (range 3–21). The mean number of outpatient visits was 8.3 (range 3–14) and the mean number of days on active treatment (until treatment was reduced to four times daily chloramphenicol or equivalent) was 31.3 (range 2–67).

Other Factors Affecting Visual Outcome

Those presenting 2–3 days after the procedure (patients 1, 3 and 4) did better than those presenting immediately (Table I). The 2 who presented months afterwards (patients 2 and 10) suffered delay in diagnosis and treatment of 5 and 7 days respectively and visual outcome was poor. Patients (4, 7 and 11) in whom anterior signs such as hypopyon developed slowly, up to 2 days after the onset of symptoms, suffered shorter delays in diagnosis.

DISCUSSION

Drainage of subretinal fluid and injection of gas are now routine in many conventional retinal detachment procedures and this entry into the eye appears to have increased the risk of endophthalmitis so that it is now comparable with that of vitrectomy. Both our finding of 0.15% incidence after vitrectomy and that of 0.19% after conven-

Table II. Possible predisposing factors

Length of op.	Medical factors	Previous I/OC surgery	Per-op. complication	Prophylaxis	
				Pre-op. drops	S/C AB
1.5 h	–	–	–	N	Y
2 h	–		Suprachoroidal haemorrhage	N	Y
2 h	Recent quinsy	ICCE	–	N	Y
1.5 h	Diverticulitis	–	–	N	N/R
1.5 h	–	–	–	g.chloro(4)	Y
3 h	–	IOFB vitreolensectomy	–	g.chloro(3)	Y
1.5 h	–	ICCE; external RD ×2	–	g.chloro(4)	Y
2.5 h	Diverticulitis	External RD ×2	–	g.chloro(3)	N/R
45 min	Sickle+	External ×1; Vit. ×1	–	g.chloro(5)	Y
2.5 h	–		Lens touch	N	Y
3 h	Diabetic	–	–	g.chloro(7)	Y

I/OC, intraocular; ICCE, intracapsular cataract extraction; IOFB, intraocular foreign body; RD, retinal detachment repair; S/C AB, subconjunctival antibiotic at end of procedure; N, no; Y, yes; N/R, no record; g.chloro( ), chloramphenicol drops (number given pre-operatively).

tional repair agree with Blankenship's figure for vitrectomy.[5] The shift towards vitrectomy for difficult cases is therefore unlikely to lead to an increase in the incidence of endophthalmitis compared with that of current conventional repair procedures.

There has been controversy over the relative merits of anterior and posterior taps in diagnosing endophthalmitis.[13,14] Organisms may survive better in the posterior segment,[15] particularly in phakic eyes, because levels of antibiotic administered topically or even subconjunctivally are low here[16–19] and the vitreous, if present, is a superior culture medium. Our finding of higher rates of positive microscopy and/or culture from vitreous samples (3/4) than from aqueous (1/3) is not statistically significant in such a small series, but nevertheless supports the principle of taking both aqueous and vitreous fluid samples in all cases.

The virulence of the organism probably had most influence on outcome, as implied by the speed of onset of endophthalmitis; the best outcome (patients 1, 3 and 4) was in those who presented at 2 or 3 days rather than immediately. Much longer delays of several months in presentation or diagnosis may, on the other hand, have allowed the exacerbation of retinal damage (and incidentally induced the phenomenon of autosterilisation of the vitreous,[20] precluding positive bacterial identification).

In spite of favourable reports of the use of intravitreal antibiotics,[21–25] there was no apparent influence on the outcome of endophthalmitis in cases where they were used. A likely explanation is that these and systemic steroids, for example, were used mainly in fulminant cases. In the vitrectomised eye, intravitreal antibiotics did not prevent eventual enucleation (patients 5 and 11), although silicone oil tamponade (patients 3, 8 and 9) may have had a protective effect.

We have identified accepted risk factors for infection[26,27] in 10 of our cases. The only patient with no risk factors and full prophylaxis (patient 5) developed infection with *Proteus*, a virulent organism which has commonly led to disastrous endophthalmitis.[3,4] Eight of our patients had two or more possible risk factors (Table I). Certain pre-operative medical risk factors such as diabetes, sickle-cell disease, chronic alcoholism and immunosuppression are clearly identifiable. The risks posed by other conditions should be weighed up individually; for example bacteraemia was thought to be a possible consequence of active diverticulitis in 2 cases and of a recent quinsy in another.

Previous ocular surgery is likely to be a risk factor,[26–28] especially where foreign bodies such as sutures and explants remain; scarred tissues may also be poorly vascularised and therefore unable to mount an adequate antimicrobial response. YAG capsulotomy has been shown to disrupt and reactivate sequestered pockets of *Propionobacter*[29,30] and there is a risk that further intraocular surgery may do the same.

Per-operative complications were recorded in 2 cases. Whilst lens touch is unlikely to increase the risk of endophthalmitis, the annular suprachoroidal haemorrhage that developed in patient 2 provided a fertile and stagnant site for abscess formation. The complexity and duration of each procedure is likely to be relevant since reintroduction of instruments into the eye represents a repeated risk of microbial contamination; Forster[13] established that for cataract surgery, a procedure exceeding 2 hours was a risk factor for endophthalmitis.

Bacteria have been shown to contaminate intraocular lenses[31] during cataract surgery and may similarly contaminate the surgical equipment[32] or explant. The organisms most commonly causing endophthalmitis after intraocular surgery are *Staphylococcus epidermidis* and other Gram-positive bacteria, which accounted for up to 80% of culture-positive cases in one study;[21] Gram-negative bacteria accounted for 16.7%. In our series, of the 7 patients in whom an organism was seen, 6 (86%) had Gram-positive and 1 (14%) had Gram-negative organisms. Routine peri-operative prophylaxis is intended to cover the risks of microbial contamination during the procedure, and the administration of prophylactic antibiotic drops before and after surgery is almost universal practice. Although several studies have indicated that it is effective,[10,28,33] none have been of sufficient magnitude to prove it. There is some evidence to support the use of subconjunctival broad-spectrum antibiotic at the end of surgery, but although several antibiotics reach therapeutic levels in the aqueous, vitreous penetration is generally low in the uninflamed eye.[34] Subconjunctival ceftazidime in the uninflamed rabbit eye does reach the minimum inhibitory concentration (MIC_{90}) for most Gram-negative organisms, including *Pseudomonas aeruginosa*, but the MIC_{90} values for *S. aureus* and *S. epidermidis* are only just achieved.[35] The vitreous penetration of certain cephalosporins and gentamicin is increased in inflammation[36] and in previously operated eyes in man.[17,37] Cefuroxime has greater activity than ceftazidime against the Gram-positive organisms[38] which most commonly cause endophthalmitis, but there is less published information about its intraocular penetration after subconjunctival injection.[39] Gentamicin, which is commonly used,[40] is again effective against staphylococci, but it does not reach the MIC_{90} for *Pseudomonas*[36] even in the inflamed eye and may cause conjunctival toxicity.[40] Ceftazidime and cefuroxime are the broadest spectrum, least toxic, most inexpensive antibiotics for routine subconjunctival prophylaxis.

In complicated cases with additional medical and surgical risk factors such as those discussed above, there is a strong case for giving supplementary prophylaxis in the form of a systemic antibiotic with good ocular penetration. Ciprofloxacin, a fluoroquinolone, has been shown in two studies in humans[41,42] to reach the MIC_{90} in the vitreous for several bacteria (including *Bacillus* but not *S. aureus* or *Pseudomonas*) after an oral dose of 750 mg and more reliably after two doses. It is also available as an intravenous infusion (200 mg). Imipenem, a third-generation cephalosporin, given in a dose of 1 g intravenously,

also achieves bactericidal levels in the vitreous, peaking at 2–3 hours after administration; it reaches the MIC_{90} for *S. aureus* and most Gram-negative organisms but not for *Pseudomonas* or *Proteus*.[43] No antibiotic fulfils all the requirements for prophylaxis in the uninflamed eye, but ciprofloxacin and imipenem are the best currently available alternatives. We recommend the use of systemic ciprofloxacin or imipenem before or during vitreoretinal surgery if there are risk factors such as diabetes, chronic alcoholism or multiple previous surgery, or if the duration of the procedure is longer than 2 hours.

The visual outcome remains poor, particularly after vitrectomy, because of pre-existing retinal damage. Virulent pathogens rapidly initiate severe inflammatory damage, which at this site is not readily amenable to effective treatment. Improved prophylaxis appears the best approach for minimising the risk of poor outcome secondary to postoperative endophthalmitis.

Key words: D-ACE, Endophthalmitis, Prophylaxis, Risk factors, Vitrectomy.

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