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A 10-year Review of Microbial Spectrum of Post-cataract Surgery Endophthalmitis in Hong Kong Chinese

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Introduction

Cataract surgery is the most commonly performed ophthalmic operation. From intracapsular to extracapsular cataract extraction and phacoemulsification, from aphakia to implantation of foldable intraocular lens, the surgical outcome after cataract surgery has been improving continually.

Postoperative acute endophthalmitis, with an estimated incidence of 0.07 to 0.26% worldwide [1-3], is one of the most serious complications after cataract surgery which may result in profound visual impairment after recovery. Studies have been conducted to identify the risk factors and possible prophylactic measures to reduce its incidence [4]. However, information regarding epidemiology of this condition and its microbial spectrum in the Chinese population is lacking. There has been no large study to date that aimed to investigate the association of the type of causative microorganisms and final visual outcome.

The primary objective of this study, therefore, was to find out the spectrum of causative microorganisms of post-cataract extraction endophthalmitis in the Hong Kong Chinese population and to compare with the post-cataract endophthalmitis case series in the literature worldwide. Any association between the causative microorganism and final visual outcome would be investigated and analyzed. We also aimed to make recommendations on the management of postoperative endophthalmitis in order to maximize visual outcome.

Materials and Methods

In this study, all the cases with a clinical diagnosis of endophthalmitis and a history of cataract surgery in the same eye within 6 weeks, under the care of the New Territories West Cluster (NTWC) Ophthalmic Team in the past 10-year period (July 1999 – June 2009), were recruited. The NTWC Ophthalmic Team served a catchment population size of one million people in Hong Kong, and was responsible for 1/6 of all cataract cataract surgeries performed by the public sector in 2007.

Cataract surgeries were performed by the NTWC ophthalmic surgeons at Tuen Mun Eye Centre, Tuen Mun Hospital, with a minority of cases referred from other hospitals in Hong Kong. Cases were retrieved through the Computerized Clinical Management System.

Patients with clinical features of postoperative endophthalmitis, including corresponding symptoms (increasing pain and blurring of vision) and signs (drop in visual acuity, hypopyon, anterior chamber or vitreous opacity obscuring second order retinal arterioles), were managed according to the guidelines from Endophthalmitis Vitrectomy Study (EVS) whenever appropriate. Early vitrectomy was arranged for patients with a presenting visual acuity of light perception or worse, while intravitreal antibiotic injection was performed for those with better visual acuity [5]. No patients had a history of uveitis or underlying ocular disease limiting the visual acuity to 6/30. The time of presentation was divided into 3 groups: acute (within 7 days), subacute (8-14 days) and delayed (15 days or later).

The diagnosis of postoperative endophthalmitis was confirmed microbiologically from intraocular samples from aqueous and/or vitreous taps obtained before intravitreal administration of antibiotics. The gold standard of microbiological diagnosis was a positive culture whereby the causative microorganism was well delineated with biochemical tests. Direct microscopy with adjuvant staining was also routinely performed in case the infective load was not sufficient for a positive culture.

The clinical outcome measures were best corrected visual acuity (BCVA) and ocular complications including retinal detachment, macular scarring or phthisis bulbi. BCVA was measured on Snellen's chart, but converted to the logMAR equivalent for statistical analysis.

Comparing the clinical outcome associated with infections by different groups of microorganisms, analysis of variance (ANOVA) was used for BCVA, and chi-square test was used for ocular complications. The benefit of systemic antibiotics was evaluated with 2-tailed t test for BCVA on the logMAR scale, and chi-square test for ocular complications.

An extensive review of the literature was performed to compare the microbial spectrum of post-cataract surgery acute endophthalmitis in international case series. Relevant studies were identified on Medline using the keywords "cataract extraction", "endophthalmitis" and "microbiology". This allows comparison of the microbial spectrum of postoperative endophthalmitis in the Hong Kong Chinese population with international data.

Results

Incidence and demographic data

In this 10-year period, 40 cases with clinical features of post-cataract surgery endophthalmitis were managed, in which 32 cases had

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had cataract surgery performed by the NTWC Ophthalmic Team and the rest referred from other hospitals. Among the total of 18473 cataract surgeries performed by the NTWC Team in this 10-year period (June 1999 – July 2009), the incidence of postoperative endophthalmitis was 0.173% (32/18473), and 0.087% (16/18473) for culture proven cases.

All patients were Chinese who resided in urban settings in Hong Kong. Twenty two (55.0%) patients were females and 18 (45.0%) were males. The mean age of cataract surgery was 73.4 ± 11.5 years.

Clinical features

The time of and clinical features upon presentation of endophthalmitis were recorded. The median time of presentation was 7 days (range 1-41days). Twenty-two cases had an acute presentation (55.0%), 8 cases subacute (20.0%) and 10 cases delayed (25.0%). Thirty three patients complained of ocular pain on presentation (82.5%).

Microbiological diagnosis

Of the 40 cases with clinical features of postoperative endophthalmitis, 19 cases (47.5%) were confirmed microbiologically by a positive culture. Vitreous tap was attempted in all but one patient with unstable medical condition. Apart from 4 dry taps, vitreous sampling was successful in 35 cases, and the yield of a positive culture was 42.9% (15/35). Aqueous tap was performed concurrently in 29 patients, with a positive yield of 17.2% (5/29). In 4 cases the causative microorganism could only be isolated from an aqueous tap but not a vitreous tap.

Among the microorganisms isolated in intraocular sample, the most frequent to be isolated was *Coagulase negative staphylococcus* (6 cases, 31.6%), followed by *Staphylococcus aureus* and *streptococcus* species (4 cases, 21.1% respectively). The 3 *streptococcus* species included *streptococcus agalactiae*, nutritionally-variant *streptococcus* and *streptococcus pneumoniae*. *Enterococcus* was isolated in 3 cases (15.8%). The remaining 2 cases were caused by *pseudomonas aeruginosa* and *agrobacterium radiobacter* respectively.

Management

Intravitreal antibiotics were given in all patients after intraocular samples for culture were obtained. The choice of antibiotics was based on the principle of broad spectrum coverage. All cases received vancomycin for the coverage of gram positive bacteria. For gram negative bacteria coverage, 36 cases received amikacin, 2 cases received ceftaxidime and 1 case received gentamicin. Intravitreal dexamethasone was used concurrently in 2 cases.

Posterior vitrectomy was performed in 13 patients, in whom 6 of them had a VA of LP or worse at the time of presentation and the remaining had suboptimal clinical response after intravitreal injection. Intravitreal antibiotic injection was repeated in 3 patients.

Systemic antibiotic as an adjunctive treatment was given in 18 cases (45.0%). Levofloxacin was most frequently used (10 cases). Cefuroxime, ceftaxidime, ampicillin, cloxacillin and clarithromycin were given for the remaining 5 cases. The final visual outcomes for patients with and without systemic antibiotic treatment are compared in Table 1. No statistical difference was found for the final BCVA (p > 0.05). Ocular complication was present in 50% of cases in both groups (p > 0.05).

	Cases treated with systemic antibiotics	Cases not treated with systemic antibiotics	P value
Final BCVA (logMAR equivalent)	1.05	0.89	0.73
Ocular complications	50.0% (9/18)	50.0% (11/22)	0.62

Table 1: A comparison final visual outcomes for patients with and without systemic antibiotic treatment.

Causative microorganism and final visual outcome

The final visual outcomes associated with different causative microorganisms are compared in Table 2.

Cases of endophthalmitis caused by *enterococcus* had the worst final visual outcome. All 3 cases (100%) had a final BCVA of LP or worse and were complicated by phthisis bulbi.

Coagulase negative staphylococcus was associated with more favourable final vision. Four out of 6 cases (66.7%) achieved a final BCVA 6/30 or better. No patient in this group had no light perception. One out of 6 cases (16.7%) was complicated by macular scarring.

Cases caused by *streptococcus* species and *staphylococcus aureus* had intermediate visual outcome. For the 4 cases of *streptococcus* species, only 1 of them (25.0%) had a final BCVA of 6/30 or better, and 2 of them (50.0%) were complicated with phthisis bulbi. For the 4 cases caused by *staphylococcus aureus*, 1 of them (25.0%) had a final BCVA of 6/30 or better, 2 patients (50.0%) managing 6/60 or better. Three of them (75.0%) were complicated by phthisis bulbi.

Comparing the logMAR equivalent of final BCVA associated with the 4 main groups of microorganisms, statistical significance was found between different groups (p < 0.005). However, there was no statistically significant difference between the proportions of ocular complication associated with different microorganisms (p > 0.005).

Discussion

This study was the one of the largest reviews of the microbiological spectrum of postoperative endophthalmitis in the Hong Kong Chinese population with cases recruited throughout a 10-year period. The incidence of post-cataract surgery endophthalmitis was 0.173% for clinical diagnosis and 0.087% for culture proven cases, which was similar to international studies [1-4].

The overall yield of a positive culture from intraocular sample with a clinical diagnosis of post-cataract surgery endophthalmitis was 47.5% in this study, which was comparable to international studies (42.7-92.9%) [6-10]. Of the 19 culture positive cases in this study, 4 patients had the causative microorganism only isolated from aqueous tap but not vitreous tap. Therefore, despite the low culture yield from aqueous tap (17.2% vs 42.9% in vitreous tap), it should still be performed despite a successful vitreous tap .in order to maximize the probability of a microbiologically confirmed diagnosis.

Possible reasons for a negative culture may include insufficient amount of intraocular sample, fastidious nature of the microorganism or sterile inflammatory reaction. Exemplified by toxic anterior segment syndrome (TASS), a sterile inflammatory reaction may be difficult to be differentiated from postoperative endophthalmitis, as both share similar clinical features especially severe anterior chamber reaction including hypopyon formation. The aetiology of TASS is related to intraoperative use of irrigating fluid and viscoelastics, injection of drugs and the chemical residues on surgical instruments after sterilization. Other features suggestive of TASS include an early presentation of 24-48 hours after surgery, less prominent pain and limbus-to-limbus corneal oedema [11]. Only well-characterized as a distinct clinical entity in recent years, TASS was not frequently re-evaluated as a differential diagnosis for the culture-negative cases of this series in the early years.

	Coagulase negative taphylococcus	*Staphylococcus aureus*	*Streptococcus* species	*Enterococcus* species	P value
Final BCVA (logMAR equivalent)	0.87	1.25	1.55	2.5	0.045
6/30 or better	66.7% (4/6)	25.0% (1/4)	25.0% (1/4)	0% (0/3)	-
6/60 or better	83.3% (5/6)	50.0% (2/4)	25.0% (1/4)	0% (0/3)	-
No light perception	0% (0/6)	0% (0/4)	0% (0/4)	33.3% (1/3)	-
Ocular complications	16.7% (1/6)	75.0% (3/4)	50.0% (2/4)	100% (3/3)	0.085
Phthisis bulbi	0% (0/6)	75.0% (3/4)	50.0% (2/4)	100% (3/3)	-
Macular scarring	16.7% (1/6)	0% (0/4)	0% (0/4)	0% (0/3)	-

Table 2: A comparison of final visual outcome for different causative micro-organisms.

	Current study	Mollan SP et al. [6]	Al-Mezaine HS et al. [7]	Ng JQ et al. [8]	Pijl BJ et al. [9]	Kunimoto DY et al. [10]	Lalwani GA et al. [13]	Benz MS et al. [14]
Coagulase negative Staphylococcus	31.6%	52.5%	35.0%	46.6%	53.6%	42.9%	68.4%	37.1%
Staphylococcus aureus	21.1%	4.9%	11.1%	18.3%	12.0%	0.9%	6.8%	7.7%
***Streptococcus* and *enterococcus* species**	36.9%	24.6%	35.0%	19.1%	21.1%	11.5%	8.2%	23.1%
Gram –ve bacteria and fungi	5.0%	4.9%	11.1%	N/A*	6.0%	29.2%	9.6%	11.8%
Other bacteria and fungi	5.0%	13.1%	7.8%	16.0%	7.3%	15.5%	7.0%	20.3%

*N/A: gram –ve bacteria was included in "other bacteria and fungi" for analysis in the original study.

Table 3: A comparison of spectrum of causative organism for post-cataract surgery endophthalmitis of this case series and international studies.

However, the majority of cases (82.5%) in this study complained of eye pain on presentation, and a clustering of events characteristic of TASS was not observed. Although TASS is an important differential diagnosis to consider, the diagnosis of infective endophthalmitis is often made on clinical grounds to initiate prompt treatment. To maximize visual prognosis, treatment should not be delayed by the culture result. While a positive culture supports the diagnosis, a negative culture cannot rule out infective endophthalmitis.

Obtaining the right intraocular samples not only confirms the definitive microbiological diagnosis of endophthalmitis, it also provides guidance on the choice of antibiotics. In addition to conventional culture, diagnosis may also be reached on the genetic level with the technique of polymerase chain reaction. In a prospective study by Chiquet et al. [12] the yield of a positive culture was increased from 32% to 61% if polymerase chain reaction assays of the aqueous sample was used on top of routine bacterial culture. Previous use of intravitreal antibiotic did not seem to affect the yield. Another advantage of polymerase chain reaction is its efficiency – the time lag for the isolation of causative microorganism could be shortened to a few hours. Moreover, antibiotic sensitivity may be predicted with the detection of resistance genes using DNA microarray technologies. This is useful for advanced planning of further management or change of antibiotics.

A review of the microbial spectrum of post-cataract surgery endophthalmitis in other studies was performed and compared with the current study (Table 3) [6-10, 13,14]. In all studies, gram positive bacteria accounted for the majority. From our data, gram positive bacteria were isolated in 17 out of 19 positive cultures (89.5%). *Staphylococcus* species, typical of skin flora, accounted for 52.6% and 43.8-78.2% of all causative microorganism in the current study and international studies respectively [6-10, 13,14]. An inference from this finding is that reducing the bacterial load of the conjunctiva and periorbital skin might be useful in reducing the risk of postoperative infection. Lid hygiene should be maintained, and any pre-existing blepharitis treated before the surgery. The effectiveness of prophylactic preoperative topical antibiotics, however, has not been supported by consistent clinical evidence [4]. This may be attributed to the increasing bacterial resistance to antibiotics. In a study by Deramo VA et al., gram-positive bacteria isolated from patients with acute endophthalmitis were frequently resistant to fluoroquinolones [15].

The microbial spectrum of post-cataract extraction in our Chinese population, however, was not found to be in complete agreement with international data. It could be observed that there were a higher proportion of cases caused by *staphylococcus aureus* and *streptococcus* and *enterococcus* species in our series, with possible association with prognostic significance and implications on preventive measures.

Within the genus of *staphylococcus*, *coagulase negative staphylococcus* was found to be associated with more favourable outcome compared with their *staphylococcus aurues* counterparts. Exemplified by *staphylococcus epidermidis*, *staphylococcus haemolyticus* and *staphylococcus saprophyticus* which are common in device-related infections, the *coagulase negative staphylococcus* group carries much less virulence factors than *staphylococcus aureus* as shown by comparative genomics. In addition to coagulase and clumping factor (or fibrinogen-binding protein), *staphylococcus aureus* carries more than 20 adhesin genes and more than 30 toxin genes. This is compared with the 10 or less adhesin genes and absence of toxin genes for *coagulase negative staphylococcus* [16-17]. The virulence factors of *staphylococcus aureus* probably explain why it produces much more tissue damage and is associated with inferior visual outcome.

Streptococcus is a diverse group of gram positive cocci with different microbiological features. Until the mid 1980s, *enterococcus* had been classified as a member of streptococcus (Lancefield group D). Therefore, among the endophthalmitis case series summarized in Table 3, *enterococcus* was only considered as a discrete entity in the studies by Mollan et al. [6]; Pijl et al. [9]; Benz et al. [14] where it accounted for 1.8-4.8% of all cases. This is compared with the 15.8% of enterococcal cases in our study, and these cases were found to be associated with worse visual prognosis.

Enterococcus, well known for its resistance to multiple antimicrobial agents, was responsible for 3 cases of endophthalmitis following cataract surgery in this series. Its resistance to some antibiotics can be intrinsic or acquired. An example to the former is its intrinsic resistance to β-lactam antibiotics caused by a diminished affinity of the lower-weight penicillin-binding proteins especially PBP 5, while its acquired resistance to aminoglycosides is explained by a decreased ability of these agents to penetrate through the outer cell envelope of *enterococci*. Theoretically an agent such as vancomycin which targets the cell wall has synergistic antimicrobial effect [18]. In the enterococcal endophthalmitis case series reported by Scott et al. [19] resistance to vancomycin was not found in all 29 isolates, nor was it found in the 3 *enterococci* isolates in our series. The poor visual prognosis of enterococcal endophthalmitis, therefore, can also be contributed by its multiple virulence factors such as cytolysin, gelatinase and serine protease [18]. In an aphakic rabbit endophthalmitis model, Takashi et al tried to find out how a secreted protease contributes to the pathogenesis of post-cataract endophthalmitis caused by *enterococcus faecalis* using 2 strains of *enterococcus faecalis*: secreted protease-positive (OG1S) and negative (OG1X) respectively. It was found that in eyes infected with OG1S, the posterior lens capsules were more severely disrupted, while inflammatory cells and cocci were detected in the anterior vitreous within 24 hours. This was associated with a significantly greater reduction in ERG b-wave amplitude than OG1X. By 48 hours, profound disruption of the retina architecture was seen with infection caused by OG1S [20].

As the endophthlamitis cases caused by *enterococcus* were associated with worse visual outcome, a more aggressive management strategy may be considered for these cases. For example, the threshold for posterior vitrectomy may be lowered should *enterococcus* be isolated from intraocular samples. It is even more preferable to be able to identify high-risk patients and implement targeted preventive measures. *Enterococci* are facultative anaerobes survive in a wide array of environments outside the original gastrointestinal reservoir. Multiresistant strains are increasingly found in hospitals and nursing homes. Patients susceptible for enterococcal nosocomial infections are those who are institutionalized, with prolonged hospital stays, multiple medical problems or various immune compromised conditions, as well as those with prior antibiotic therapy [18]. These high-risk patients may be identified before cataract surgery and extra precautions should be exercised apart from the usual aseptic procedures. In particular, we recommend that intraoperative intracameral antibiotic be administered routinely in these patients.

Consistent with the Endophthalmitis Vitrectomy Study (EVS) [5], systemic antibiotic as an adjunctive treatment was not found to affect final visual outcome in this study. However, it is worthy to note that in many cases different antibiotics were given intravitreally and systemically. If the same group of antibiotic had been given systemically, the maintenance of effective intravitreal level of antibiotic could probably be prolonged by reducing the outward diffusion gradient. The ESCRS group also suggested that oral probenecid be added to inhibit the outward transport of antibiotics across the retinal capillary endothelial cells and proximal renal tubules [21].

The role of steroid in post-cataract surgery endophthalmitis is controversial. While it weakens immune response for the control of microbial proliferation, it also dampens down detrimental inflammation mediated by cytotoxic cytokines and infiltrating leukocytes. Inflammation may be further perpetuated by the release of antigens due to bacterial disintegration by antibiotics. Concerning the mode of steroid administration for endophthalmitis, both intravitreal and oral routes have been proposed. For intravitreal injection, separate syringes from antibiotics are advisable [22]. Oral prednisolone (1mg/kg body weight) one day after intravitreal antibiotic has also not been shown to affect the control of infection in bacterial endophthalmitis [23]. In our series, however, dexamethasone was only included in the intravitreal injection regime in 2 patients, who's final VA, turned out to be LP and 6/60 respectively. No conclusion can be drawn due to the small number of cases.

As postoperative endophthalmitis is a relatively uncommon complication, the number of cases was small despite a recruitment of 10 years of cases. This limits the power of statistical analysis of different factors on various parameters of clinical outcome. An evaluation of a larger number of pooled cases in the Chinese population would be recommended for future studies.

Based on the findings of the study, we hope to make recommendations regarding the diagnosis of management of postoperative endophthalmitis. First of all, intraocular samples from both aqueous and vitreous taps are advised in order to maximize the culture yield. The dominance of cases by gram-positive cocci typical of the bacterial skin flora also raised the importance of maintenance of lid hygiene and treatment of pre-existing blepharitis in order to reduce the bacterial load of the surgical field. Compared with international studies, the microbial spectrum of postoperative endophthlamitis of the Hong Kong Chinese population was found to consist of a higher proportion by *enterococcus* and *staphylococcus aureus* which were significantly associated with worse visual outcome. A lower threshold for aggressive management such as posterior vitrectomy might be beneficial for these cases. It is also important to identify high-risk patients and exercise appropriate precautions. Due to the limited number of cases, the role of adjunctive treatment is inconclusive. However, steroid therapy is generally safe after infection has been controlled and systemic antibiotic of the same group as that given intravitreally may be considered. As postoperative endophthalmitis is a devastating complication which could result in long-term visual impairment, it is worth every effort to prevent its occurrence and optimize its management for the best visual outcome.

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