Featured Review Article

Redefining evidence in the management of acute post-cataract surgery endophthalmitis in India - The 2014 Adenwalla Oration, All India Ophthalmological Society

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The current evidence of postoperative endophthalmitis management in three important components of care-infection control, inflammation control, and prevention was reviewed, and their current relevance and application in an Indian context were evaluated. The publications from India indicated that Gram-negative bacterial and filamentous fungal infections are relatively higher. There are increasing instances of resistance to ceftazidime by Gram-negative microorganisms. Intravitreal dexamethasone limits inflammation in bacterial endophthalmitis when given together with the intravitreal antibiotics. Intracameral antibiotic could reduce postcataract surgery infection at least in less rigorous surgical environment. Systematic collection of data and periodic evaluation of the current practice against the new evidence are necessary to prevent or treat postcataract surgery endophthalmitis.

Key words: Cataract surgery, endophthalmitis, evidence, management

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_755_17

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Postoperative endophthalmitis is an inflammatory condition of the eye, presumably due to an infectious process, usually from bacteria and fungi that enter the eye in the perioperative period. The incidence of postoperative endophthalmitis after cataract surgery has decreased dramatically over the last decades, from over 2% in 1920 to the current incidence of around 0.05%.[1] In three large Indian cohort studies, the incidence of endophthalmitis was <0.1%.[2-4] This is due to increase in our knowledge in the understanding of the cause, treatment, and prevention of this dreaded complication of cataract surgery. The increase in our knowledge is based on a number of studies, several seminal publications, and evidence. They are the basis of the current standard of care. However, the standard of care changes from time to time as new evidence emerges. In this communication, the current standard of care in acute postcataract surgery endophthalmitis was examined vis-a-vis the newly generated evidence in an Indian context.

There are three components of postoperative endophthalmitis care-infection control, inflammation control and prevention of such an event. These three components are described subsequently.

Infection control

The mainstay of infection control in infective endophthalmitis is injection of intravitreal antibiotics. The current recommendation is to inject two antibacterial antibiotics, one that acts against Gram-positive microorganism and the other that acts against Gram-negative microorganism. The initial suggestion of intravitreal antibiotic emerged from the seminal works of Peyman *et al*.,[5] but over years, this has changed from aminoglycosides (gentamicin, amikacin) to β-lactam antibiotics (fourth-generation cephalosporin-ceftazidime) for Gram-negative bacilli and from cefazolin (first-generation cephalosporin) to vancomycin (glycopeptide antibiotic) for Gram-positive cocci. Antifungal antibiotic has never been considered as the primary care because of lower incidence of postcataract surgery acute fungal endophthalmitis.

The current practice of infection control is guided by the Endophthalmitis Vitrectomy Study (EVS).[6] The EVS was a prospective randomized trial that studied the utility of systemic antibiotics and benefit of immediate vitrectomy in acute postcataract surgery endophthalmitis. The study showed that systemic antibiotics did not alter the outcome; instead, the presenting vision influenced the decision for immediate/deferred vitrectomy. The EVS also identified Gram-positive cocci as the most common infecting organism and *Staphylococcus epidermidis* was the most common Gram-positive cocci.[7] The EVS recommended the treatment of acute postcataract surgery endophthalmitis as follows: (1) all patients receive two intraocular antibiotics (vancomycin 1 mg in 0.1 ml against Gram-positive cocci, and ceftazidime 2.25 mg in 0.1 ml against Gram-negative bacilli), (2) vitreous biopsy be

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Manuscript received: 19.08.17; Revision accepted: 07.09.17

Cite this article as: Das T. Redefining evidence in the management of acute post-cataract surgery endophthalmitis in India - The 2014 Adenwalla Oration, All India Ophthalmological Society. Indian J Ophthalmol 2017;65:1403-6.

done (and microbiology study, where possible) in patients with presenting vision of hand motions or more, and vitrectomy be done for patients with presenting vision of light perception or less (vitrectomy in all diabetics irrespective of presenting vision), and (3) oral corticosteroids (1 mg/kg body weight and tapered after a 7–10 days) be started a day after the intravitreal intervention (with biopsy or vitrectomy).

We looked at these data in Indian context and evidence. Our published data showed that while Gram-positive cocci was indeed the most common infecting organism in postcataract surgery endophthalmitis, Gram-negative bacterial infection occurred in quarter of the time, and fungal infection occurred in close to one-fifth of time.[8] There are similar reports from two Asian countries, China and Singapore.[9,10] Table 1 compares the Asian reports (India, China, and Singapore) with the North American EVS[6] and European Society of Cataract and Refractive Surgeons (ESCRS) reports.[11]

We also observed that while vancomycin had a close to 100% sensitivity toward Gram-positive cocci, ceftazidime sensitivity toward Gram-negative bacilli was not >61%. This could relate to different kind of Gram-negative organisms, predominantly *Proteus mirabilis* in the EVS and *Pseudomonas aeruginosa* in our study. The Chennai group and we also compared the infecting microorganisms in different time periods the Chennai group between 2001 and 2007 and we between 1999 and 2012.[4,13,14] These studies showed that Gram-negative infection is consistently between 30% and 40% and that *P. aeruginosa* continues to be the predominant Gram-negative infection [Table 2].

Our current data also suggest increasing resistance of *P. aeruginosa* to ceftazidime[15] and sensitive to imipenem.[16] Should this be true, imipenem should replace ceftazidime as the primary drug of choice for intravitreal antibiotic against Gram-negative bacteria. Imipenem inhibits cell wall synthesis of various Gram-positive and Gram-negative bacteria. It remains very stable in the presence of β-lactamase (both penicillinase and cephalosporinase) produced by some bacteria and is a strong inhibitor of β-lactamases from some Gram-negative bacteria that are resistant to the most β-lactam antibiotics (such as ceftazidime).[17]

Inflammation control

Inflammation is an important component of infective endophthalmitis. The EVS used oral corticosteroid (1 mg/kg of body weight) a day after the intravitreal antibiotics therapy and tapered over a period of time. Intravitreal corticosteroid was not a part of the EVS protocol. Animal studies have shown the utility of intravitreal corticosteroids in bacterial endophthalmitis.[18] Our prospective randomized trial of intravitreal dexamethasone in postoperative and traumatic endophthalmitis study demonstrated that intravitreal

Table 1: Microbiology of endophthalmitis

Summary	Microorganism	EVS[7]	ESCRS[12]	India[8]	China[9]	Singapore[10]
GPC EVS - 94% ESCRS - 95% India - 53% China - 74% Singapore - 77%	*S. epidermidis*	70.0%	45.4%	35.2%	45.5%	57.14%
	S. aureus	10.0%	9.1%	0.8%	12.4%	4.76%
	Streptococcus spp.	11.2%	35.4%	10.3%	6.2%	9.52%
	Others	1.2%	9.1%	9.5%	9.8%	4.76%
GNB EVS - 6% ESCRS - 0% India - 26% China - 13% Singapore - 13%	*Proteus* spp.	6.0%	-	0.9%	13.4%	4.76%
	Pseudomonas spp.	-	-	19.8%	-	4.76%
	Others	-	-	5.3%	-	4.76%
Fungi		-	-	16.7%	12.7%	-

EVS: Endophthalmitis Vitrectomy Study, ESCRS: European Society of Cataract and Refractive Surgeons, *S. epidermidis*: *Staphylococcus epidermidis*, *S. aureus*: *Staphylococcus aureus*, GPC: Gram postivive cocci, GNB: Gram negative bacilli

Table 2: Comparison of the spectrum of microorganism in two Indian institutions in different time frames

Summary	Microorganism	Chennai*[4,13]		Hyderabad**[14]	
		2000	2010	1999	2013
GPC Chennai - 32.9 and 44.8% Hyderabad - 46.8% and 50.0%	*S. epidermidis*	11.5%	13.8%	35.7%	24.2%
	S. aureus	7.5%	8.5%	0.8%	3.6%
	Streptococcus	1.7%	4.2%	10.3%	21.4%
	Others	9.2%	9.5%	9.5%	12.0%
GNB Chennai - 41.7% and 43.8% Hyderabad - 26.2% and 35.9%	*Proteus*	-		0.9%	
	Pseudomonas	16.1%	14.8	19.8%	22.2%
Fungus Chennai - 21.8% and 7.1% Hyderabad - 16.7% and 8.1%	*Aspergillus*	10.9%	4.2%	13.5%	3.2%

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dexamethasone reduced inflammation faster in both culture-positive and culture-negative endophthalmitis compared to the eyes that did not receive intravitreal dexamethasone and that it did not affect the final visual outcome.[19] We also demonstrated that intravitreal triamcinolone dramatically reduces inflammation in recalcitrant situation where the eye is already sterilized by the sensitive intravitreal antibiotic.[20]

We recommend and routinely use intravitreal dexamethasone (400 µg in 0.1 ml) in all cases of postcataract surgery acute endophthalmitis (presumably all acute infections are caused by bacteria) along with intravitreal antibiotics. We have reported the benefit of this treatment strategy, vitrectomy plus intravitreal antibiotics, and dexamethasone in two different cluster endophthalmitis, where more than half patients regained good vision (>20/40) and three-quarters of them regained ambulatory vision (>20/100)[21,22] [Table 3].

Infection prevention

Primarily based on the seminal study of Speaker *et al*.,[23] the current strategy of infection prevention is directed to the patient's conjunctival flora as much as controlling the environment and medical supply. In an experimental study, we have shown that vancomycin contact reduces *S. epidermidis* adherence on poly-methyl methacrylate intraocular lens.[24] The ESCRS studied the benefits of intracameral cefuroxime in prevention of acute bacterial endophthalmitis.[12] They chose cefuroxime because of its known activity against Gram-positive bacteria and the predominant infecting organisms in postcataract surgery endophthalmitis (In the ESCRS analysis, 95% of infecting organisms were Gram-positive cocci). This study recommended routine use of intracameral antibiotics such as cefuroxime at conclusion of cataract surgery to prevent or significantly reduce infection in these patients. Several recent studies from the USA, the Middle East, and India have shown benefits of intracameral antibiotics in cataract surgery.[25-27] Other intracameral antibiotics used at various times are cefazolin, vancomycin, and moxifloxacin.

We examined this recommendation in a prospective study where over 7000 consecutive patients did not receive intracameral cefuroxime (Group 1) and another 7000 plus consecutive patients received intracameral cefuroxime (Group 2). Culture- positive endophthalmitis was 0.09% (clinical endophthalmitis, 0.155%) in the eyes that did not receive intracameral cefuroxime, and it was 0.04% (clinical endophthalmitis, 0.108%) in the eyes that received intracameral cefuroxime. While the culture-positive endophthalmitis rate reduced by half, the odds of clinically diagnosed postoperative infection were 1.42, should one chose not to inject intracameral cefuroxime; this was not statistically significant.[28] Equally important was the fact that six of seven microorganisms were Gram-positive cocci in Group 1 (no intracameral group), and two of three microorganisms were Gram-negative bacilli in Group 2 (intracameral group). This study did not find compelling reasons to recommend routine use of intracameral cefuroxime during cataract surgery. While there are mounting evidence for routine use in all cases,[29,30] there are also logics against such indiscriminate use.[31] In the absence of further evidence, one could consider intracameral antibiotic in high-risk situations such as diabetics, one-eyed individuals, prolonged surgery, vitreous loss during cataract surgery, very elderly persons, and immunocompromised patients (some of them defined by the EVS[6]) to avoid an overuse and cause bacterial resistance later.

Table 3: Treatment outcome of cluster endophthalmitis

Treatment regimen: PPV + intravitreal antibiotics + intravitreal dexamethasone	2005 (*n*=7), *n* (%)	2010 (*n*=11), *n* (%)
>20/40	4 (57.1)	7 (63.6)
>20/100	5 (71.4)	9 (81.8)

PPV: Pars plana vitrectomy

Conclusion

Effective treatment of a given case of endophthalmitis, in specific, and prevention of postoperative endophthalmitis, in general, are necessarily constant goals of every ophthalmic surgeon. The current evidence suggests good outcome when infection is detected early and treated appropriately. There is agreement that intravitreal antibiotics are the mainstay of treatment in infective endophthalmitis. However, due to changing profile of sensitivity, one could consider a change in the selection of primary intravitreal antibiotics.[32] There is also a general consensus that systemic therapy does not necessarily add additional benefit. However, contrary to the EVS recommendation of confining immediate vitrectomy to the eyes with light perception or less, more often immediate vitrectomy is preferred irrespective of the presenting vision.[9] Prevention of such a dreaded complications is equally important. In addition to the meticulous preparation of eye and the skin around the eye with povidone-iodine, should one consider injecting an intracameral antibiotic? Such an attempt was done earlier in South India community cataract surgical camps with a reported beneficial effect.[33] While intravitreal gentamicin used earlier could be replaced with another antibiotic today, the chosen antibiotic should have broader coverage for both Gram-positive and Gram-negative organisms. Close to 70% of cataract surgeons who responded to a 2012 Singapore nationwide survey admitted to not using any intracameral antibiotic. While the reasons were the fear of toxicity, the effort of antibiotic preparation, and additional cost, many did not agree with the benefit of this procedure too.[34] At the same time, 54% stated to consider to using intracameral antibiotic routinely should such a ready-to-use preparation were available. Currently, cefuroxime (Aprokam™ by Thea) and moxifloxacin (Promox™ by Aurolab) are commercially available in Europe and India, respectively. While intracameral cefuroxime is now a standard of care in Europe, one has to wait if this becomes a standard of care globally. It is necessary to weigh the benefit against the risk of emergence of resistant strains.

Financial support and sponsorship

Hyderabad Eye Research Foundation, Hyderabad, India.

Conflicts of interest

There are no conflicts of interest.

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