Pharmacogn J. 2024; 16(5): 1188-1191
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Effects of Bacteriophage in Postoperative Endophthalmitis Caused by *Staphylococcus aureus*

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ABSTRACT

Postoperative endophthalmitis is a serious complication of cataract surgery. It may leads to vision loss. The most common organism cause endophthalmitis is gram-positive bacteria, mainly *Staphylococcus aureus (S. aureus)*. To prevent postoperative endophthalmitis, eye drops or intracameral administration of antibiotic agents are universally used. In recent years, the trend of endophthalmitis treatment has grown rapidly. Administration of bacteriophage is a subject of research for the treatment and prophylaxis of postoperative endophthalmitis. This literature review investigates the potential of bacteriophage to provide a rapid, effective alternative to antibiotic treatments for postoperative endophthalmitis caused by *S. aureus*.

Keywords: postoperative endophthalmitis, bacteriophage, *Staphylococcus aureus*.

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History

- Submission Date: 02-09-2024;
- Review completed: 05-10-2024;
- Accepted Date: 10-10-2024.

DOI : 10.5530/pj.2024.16.194

Article Available online

http://www.phcogj.com/v16/i5

INTRODUCTION

Postoperative endophthalmitis is a serious complication of cataract surgery, with symptoms of eye pain and vision loss. The worldwide incidence of postoperative endophthalmitis varies from 0.02% to 0.71%. The microbial causative organisms of endophthalmitis were 85.1% by gram-positive bacteria, 10.3% by gram-negative bacteria, and 4.6% by fungi [1,2,3].

Bacteriophages are viruses that infect bacteria. Phage endolysins are peptidoglycan hydrolases produced near the end of the phage lytic cycle to degrade the cell wall and allow nascent phage particles to escape to infect the host cell [4]. Endolysins are highly specific to host bacteria and have evolved to bind to unique and important bacterial cell wall targets. In recent years, bacteriophage endolysin has attracted considerable interest as novel antibacterial agents and are being used to treat a variety of bacterial infections, as evidenced by an increasing number of studies in laboratory animals [5,6,7,8].

Postoperative Endophthalmitis

Endophthalmitis is an intraocular inflammation involving the aqueous and vitreous. Postoperative endophthalmitis is endophthalmitis caused by the entry of microorganisms into the eye after intraocular surgery. Common causative organisms of postoperative endophthalmitis are gram-positive bacteria (*coagulase-negative Staphylococcus species, Staphylococcus aureus, Streptococcus sp.*), gram-negative bacteria or fungi. Cataract surgery is a large segment of intraocular surgery, most scientific reports on postoperative endophthalmitis focus mainly on cataract surgery. Postoperative endophthalmitis is classified by onset, with acute onset occurring within 6 weeks postoperatively and chronic onset occurring more than 6 weeks postoperatively [3,9,10].

There are several risk factors for acute postoperative endophthalmitis (table 1). Acute onset postoperative endophthalmitis has a clinical picture of intraocular inflammation, often with hypopyon, conjunctival vascular congestion, corneal and eyelid edema. Patients complain of pain in the eye and experience loss of vision [3,9].

If visualization of the posterior segment is limited due to corneal inflammation or edema, B-scan ultrasound may be considered to assess the degree of vitreous opacification and to determine the presence of choroidal or retinal detachment. Confirmation by intraocular fluid culture is an important step in subsequent management. Vitreous specimens can be obtained using a needle (vitreous tap) or by vitrectomy [9,11].

Staphylococcus aureus

Staphylococcus aureus (S. aureus), is a gram-positive, cocci-shaped bacterium. *S. aureus* is a major pathogenic bacterium that causes a wide variety of clinical manifestations of disease in humans. Infections are common in both community-acquired and hospital-acquired environments. Treatment of this bacterium is challenging due to the emergence of multidrug-resistant strains, such as MRSA (*Methicillin-Resistant Staphylococcus aureus*) [12].

Pathogenesis of Endophthalmitis Caused By *Staphylococcus aureus*

The pathophysiology that contributes to *S. aureus* endophthalmitis includes 1). *S. aureus* cell wall components, 2). Quorum sensing system and biofilm formation, 3). The stress regulator σ^B, and 4). The virulence environment CodY [13].

Staphylococcus aureus cell wall components

The cell wall components of *S. aureus*, that is peptidoglycan, lipoproteins, and teichoic acid, play an important role in virulence by contributing to the stimulation of immunity. Lipoteichoic acid and peptidoglycan on the cell wall are able to activate complement, respectively, leading to the release

Cite this article: Ramadhani H, Wahyuni I, Zuhrial I, Setiawan F, Proboningrat A, Legowo D, Indriani D. Effects of Bacteriophage in Postoperative Endophthalmitis Caused by *Staphylococcus aureus*. Pharmacogn J. 2024;16(5): 1188-1191.

Tabel 1. Risk factor for acute postoperative endophthalmitis[9].

Preoperative	Durante operative	Postoperative
Diabetes mellitus	Application of 2% xylocaine gel drops prior to povidone-iodine administration	Postoperative wound leak
Immunocompromise	Prolonged surgery	Vitreous incarceration
Chronic blepharitis	Secondary intaocular lens (IOL)	
Lacrimal infection	Posterior capsule rupture	
Use of contaminated eye drops	Loss of vitreous	
Use of contaminated contact lenses	Contaminated irrigation fluid	
Use of prostheses in the contralateral eye		

of cytokines and chemokines by monocytes and macrophages. Wall teichoic acid (WTA), a major polyanionic polymer component of the *S. aureus* cell wall, is critical for virulence manifestation in endophthalmitis, and has been targeted with small molecule inhibitors of its biosynthesis. Proteins from cell wall A bind to immunoglobulin G (IgG), coat the cell surface and prevent neutrophils from binding, thus interfering with phagocytosis. Protein A is also used by *S. aureus* to evade antigen-specific B cell responses. It is identified as a B cell sensitizer for the recognition of TLR2-activated lipopeptides that promote T cell-independent B cell proliferation, without inducing immunoglobulin M (IgM) secretion. It also activates clone-specific T cells. Protein A also affects IL-1 release and increases TNF-α and nitric oxide production in vivo through macrophage activation [13].

Quorum sensing system and biofilm formation

Staphylococcus aureus exists in alternative physiological states depending on environmental conditions/stressors, and bacterial numbers, i.e. planktonic (free-living, mobile) and sessile (quiescent, biofilm-forming) states that correlate with changes in bacterial physiology and virulence expression. There are regulatory mechanisms involved in the transition from planktonic to biofilm phenotype. The accessory gene regulatory system (agr) is a key determinant of cell density-dependent regulation of gene expression by *S. aureus*. The agr operon encodes an autoinducer peptide (AIP). AgrA triggers increased transcription of RNA II and RNA III. *Staphylococca*l Accessory Regulator (SarA) complements agr in regulating virulence gene expression. SarA is a DNA-binding protein that activates target genes by binding to conserved A/T-rich recognition motifs of selected promoters. SarA promotes the synthesis of fibronectin and fibrinogen-binding proteins involved in bacterial adhesion, and the synthesis of α-, β- and δ-toxins involved in tissue lysis and infection spread. SarT which is repressed by sarA and agr, suppresses alpha toxin expression, highlighting the complexity of virulence regulation in *S. aureus* [13].

The stress regulator σ^B

σ^B regulation includes more than 100 genes involved in stress response, cell envelope biosynthesis, intermediary metabolism and other signaling pathways. Virulence-related σ^B-regulated genes are those that contribute to bacterial aggregation and protection against the types of oxidative stress that can result from PMN engulfment and antibiotic exposure. Based on microarray analysis of the transcriptional profiles of different *S. aureus* strains and their respective isogenic σ^B mutants, σ^B appeared to fine-tune virulence factor production in response to a changing environment. σ^B was found to increase the expression of many adhesins, and suppress exoprotein and toxin production, and thus would likely act in opposition to RNA III, the effector molecule of agr [13].

The virulence environment CodY

CodY has been found to link *S. aureus* virulence to its metabolic state, and similar regulators may exist for most pathogens. CodY is a GTP-binding global regulator, first identified in Bacillus subtilis. In those hosts, it senses the nutrient environment and regulates the biosynthesis of catabolic enzymes, and the production of competence factors for DNA sequestration. In *S. aureus*, CodY affects the regulation of RNA II and RNA III expression in the agro operon, and consequently, affects the expression of alpha toxin and possibly other toxins. It also regulates PIA production, in addition to its role in regulating capsule production. In addition to its indirect role in regulating virulence gene expression through agr, codY also directly regulates many transcription units associated with amino acid biosynthesis, macromolecular transport, and virulence. CodY is responsive to GTP and branched-chain amino acid (BCAA) concentrations in the environment. Isoleucine is the major ligand for CodY, and when it is above a critical threshold, causes CodY to repress transcription of target genes. Based on studies in other organisms, such as S. pyogenes, it is suggested that the requirements for CodY activation may be met in the bloodstream and other tissues, resulting in a CodY-induced lag in virulence expression, in an attempt to stably coexist with the host [13].

Bacteriophage

Bacteriophages or phages are viruses that exclusively infect bacteria in their life cycle. The main structure of a classical phage consists of a head and a tail. The head (or capsid) is a protein shell in the shape of an icosahedron containing the phage DNA as dsDNA. The tail generally has six tail fibers that hold receptors to recognize attachment sites on the bacterial cell surface [14,15].

The practice regarding bacteriophages has been around for almost a century. Frederick Twort first described the characteristic zones of lysis associated with phage infection in 1915, however it was Felix d'Herelle who identified the cause of this phenomenon, attributing the plaque to a bacterial viruses and coining the term "bacteriophage". d'Herelle conceived the idea of using phages therapeutically and was responsible for the first documented clinical use of phages in 1919 at the Hôpital des Enfants-Malades in Paris where phages were successfully used to treat 4 pediatric cases of bacterial dysentery [14,15,16,17].

The bacteriophage lytic life cycle ends with the death of the bacterial cell, so the phage becomes a natural killer of bacteria. Lysis occurs by one of two basic mechanisms. On the one hand, phages with single-stranded genomes encode lysis effectors that inhibit bacterial peptidoglycan biosynthesis. On the other hand, the release of phage progeny in double-stranded DNA (dsDNA) phages is mediated by two proteins, holin and endolysin, which are responsible for cell envelope disruption. Once the lytic life cycle is complete and virion particles mature inside the bacterial cell, holin forms pores in the inner cell membrane, allowing endolysin access to the cell wall. The endolysin molecules then degrade the peptidoglycan, causing osmotic lysis of the cell. In addition, some phages can utilize the host cell secretion machinery (Sec system) to release their endolysin and also encode holin (pinholin) involved in proton motive force dissipation to activate the secreted endolysin. Virion-associated peptidoglycan hydrolases (VAPGHs) are structural components of virion particles and participate in the initial steps of infection by slightly degrading peptidoglycan to allow entry of phage genetic material into bacterial cells. Both types of lytic proteins, endolysins and VAPGHs, are useful as antimicrobials due to their potential to degrade peptidoglycan, resulting in cell lysis when added exogenously [14,15].

Prophylaxis and Treatment of Endophthalmitis

To prevent post-cataract surgery endophthalmitis, eye drops or intracameral administration of antibiotic agents are universally

used. The ESCRS study recommends administration of intracameral cefuroxime (1.0 mg in 0.1 ml) during cataract surgery to prevent postoperative endophthalmitis. Cefuroxime is a second-generation cephalosporin that is susceptible to gram-positive cocci. In India, the use of intracameral moxifloxacin (0.5 mg in 0.1 ml) was effective in reducing the occurrence of endophthalmitis. The current pattern of antibiotic prophylaxis in cataract surgery in India is 90% using topical antibiotics before surgery, 40% using intracameral antibiotics, and 94% using topical antibiotics after surgery [18,19].

Intravitreal antibiotic therapy is the current standard therapy in postoperative endophthalmitis. The initial choice of intraocular antibiotic therapy before culture results are available is always empirical. Endophthalmitis Vitrectomy Study (EVS) recommendations for current treatment plan is a combination of vancomycin (1 mg/0.1 mL) and ceftazidime (2.25 mg/0.1 mL). It is effective against a broad spectrum of bacteria that cause acute onset postoperative endophthalmitis. In patients with postoperative endophthalmitis with only light perception visual acuity and possibly in diabetic patients despite better visual acuity, pars plana vitrectomy should be performed [3,9].

Administration of Bacteriophage In Ocular Diseases Including Endophthalmitis

Phage lytic proteins are effective under in vitro conditions, it is also important to prove that phages can be active in vivo. Various animal models have been created to mimic infections caused by *S. aureus*. These animal models, using lytic proteins, can be used to test the efficacy of therapeutic and prophylactic treatments for infections. Several studies have suggested that bacteriophages can be used as prophylaxis or therapy in various diseases and bacteria [15,17].

Overuse of antibiotics can increase the risk of developing drug-resistant bacterial infections. The use of bacteriophages could be beneficial in ocular diseases where inflammatory mechanisms can lead to scarring, tissue damage and subsequent vision loss (endophthalmitis, panophthalmitis, keratitis and, more recently, age-related macular degeneration) [20].

Several therapeutic and prophylactic effects of bacteriophage have been described. Fukuda et al. in 2012 reported bacteriophage KPP12 eye drops treatment for mice model *Pseudomonas aeruginosa (P. aeruginosa),* keratitis significantly reduced neutrophil infiltration and increased bacterial clearance in the infected cornea. Bacteriophage eye drops could be a potential adjunctive or alternative therapeutic form in the treatment of infectious keratitis caused by resistant bacteria [21]. Fadlallah et al in 2015 reported a case of a 65-year-old woman with left eye corneal abscess and interstitial keratitis due to VRSA. *S. aureus* bacteriophage SATA-8505 (ATCC PTA-9476) was used for four weeks at Phage Therapy Center, Tbilisi, Georgia. Bacteriophage eye drops were effective against VRSA and concluded that it could be used as a novel adjunctive therapeutic agent to treat infectious keratitis caused by are antibiotic-resistant bacteria [22]. Furusawa et al in 2015 reported topical solution of Bacteriophage cocktail ΦR18 and ΦS12–1 from wastewater samples could reduce *P. aeruginosa* in mouse model [23]. Urban-Chmiel et al., 2020 investigated the antibacterial effect of bacteriophage eye drops against *Staphylococcus sp.* isolated from dogs with bacterial conjunctivitis and found 100% sustained and consistent antibacterial activity at the titer of 108 PFU/ml of eye drop solutions [24]. Rahimzadeh et al in 2021 conducted an *ex-vivo* evaluation of in-situ gel eye drop formulation including bacteriophage for the treatment of keratoconjunctivitis cause by *P. aeruginosa* in rabbit eyes. They concluded that the in-situ gel-forming method could be used to extend the release of bacteriophage for the treatment of ocular infections [25].

Kishimoto et al in 2018 in Japan demonstrated the therapeutic potential of intravitreal bacteriophage ΦEF24C-P2 injection in a mouse model of endophthalmitis caused by vancomycin-sensitive (EF24) or vancomycin-resistant (VRE2) strains of *Enterococcus faecalis (E. faecalis)*. Phage ΦEF24C-P2 induced rapid and extensive bacterial lysis in reduction assay using EF24, VRE2, and clinical isolates from patients with *E. faecalis*-associated postoperative endophthalmitis [26]. Intravitreal injection of three newly isolated enterococcal bacteriophages, phiEF7H, phiEF14H1, and phiEF19G were able to lyse a broad range of *E. faecalis*, including strains derived from postoperative endophthalmitis and vancomycin-resistant *E. faecalis* in mice. Six hours after injection the phages, intraocular viable bacterial counts and neutrophil infiltration reduced [27]. Another study conducted by Kishimoto et al in 2021 in Japan reported prophylactic bacteriophage therapy against endophthalmitis caused by Enterococcus sp. with the results that injection 2×10^9 PFUs of intracameral bacteriophage phiEF24C-P2 did not cause retinal dysfunction and suppressed postoperative endophthalmitis in rabbits [28].

CONCLUSION

The trend of endophthalmitis treatment and prophylaxis has increased rapidly. Antibiotic resistance is rapidly increasing worldwide, leading to increased morbidity and mortality with ineffective treatment of antibiotic therapy. *S. aureus* is the main cause of bacterial eye infections and has acquired resistance to several antibiotics, however, phage therapy has been proven to be effective in such conditions. Administration of bacteriophage is a subject of research for the treatment and prophylaxis of postoperative endophthalmitis. The efficacy and safety of phage formulations for the prevention and treatment of bacterial eye infections, including endophthalmitis remains to be established in clinical trials.

AUTHOR CONTRIBUTION

All authors contributed to article preparation and revision and have collectively assumed responsibility for all aspects of this article.

ACKNOWLEDGMENT

The authors would like to extend their sincere gratitude to all individuals who supported and contributed to this review undertaking.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in this review article.

FUNDING SOURCE

There was no specific funding from governmental, commercial, or non profit entities for this article.

ETHICAL CLEARANCE

Not applicable.

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Cite this article: Ramadhani H, Wahyuni I, Zuhrial I, Setiawan F, Proboningrat A, Legowo D, Indriani D. Effects of Bacteriophage in Postoperative Endophthalmitis Caused by Staphylococcus aureus. Pharmacogn J. 2024;16(5): 1188-1191.