Bacteriophage Therapy for *Staphylococcus aureus*-Induced Postoperative Acute Endophthalmitis *In Vivo*

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Abstract

Background: Postoperative acute endophthalmitis is a rare but severe complication following cataract surgery, with bacterial pathogens such as Staphylococcus aureus being the leading cause. Despite declining incidence rates globally, visual outcomes remain poor in many cases. Recent studies have explored the potential of bacteriophage therapy to treat bacterial infections, particularly for antimicrobial-resistant strains. This study aimed to assess the therapeutic effectiveness of bacteriophage treatment in a rabbit model of S. aureus-induced acute postoperative endophthalmitis. Methods: The study employed a randomized, controlled, posttest-only design using New Zealand white rabbits. Following extracapsular lens extraction surgery, rabbits were injected with S. aureus intracamerally to induce endophthalmitis. The treatment group received additional bacteriophage therapy. Ocular inflammation was assessed by measuring two biomarkers, myeloperoxidase (MPO) and intercellular adhesion molecule-1 (ICAM-1), using enzyme-linked immunosorbent assay (ELISA) from vitreous fluid samples. Histopathological analysis of retinal and scleral structures was performed post-enucleation. Statistical analyses were conducted using independent t-tests. Results: The treatment group showed significantly lower ICAM-1 levels ($p < 0.001$), indicating reduced leukocyte infiltration and inflammation compared to the control group. MPO levels were slightly elevated in the treatment group but were not statistically significant ($p = 0.261$). Histopathological examination revealed that retinal structures in the treatment group were preserved with reduced inflammatory cell infiltration, whereas the control group displayed extensive retinal damage, including neovascularization and retinal detachment. Conclusion: Bacteriophage therapy significantly reduced ocular inflammation and tissue damage in S. aureus-induced endophthalmitis, as evidenced by lower ICAM-1 levels and better-preserved retinal structures in the treatment group. These findings suggest that bacteriophage therapy may be an effective alternative to conventional treatments for postoperative acute endophthalmitis, particularly in cases involving antibiotic-resistant bacteria. Further studies are warranted to explore its broader clinical applicability.

Keywords: Postoperative acute endophthalmitis, Bacteriophage therapy, Staphylococcus aureus, Inflammation markers, Cataract surgery

Significance | This study determined the bacteriophage therapy's potential in reducing inflammation and preserving retinal structure post-cataract surgery-induced endophthalmitis.

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Introduction

Postoperative acute endophthalmitis is one of the most severe complications that can arise following cataract surgery. Defined as an intraocular infection occurring within six weeks post-surgery, it

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poses a significant risk to visual prognosis (Rapuano et al., 2022; Simakurthy & Tripathy, 2022). Although the global prevalence is relatively low, the incidence varies by region, ranging from 0.05% to 0.3% (Choi & Chung, 2011). In China, retrospective studies over the past decade have shown a a prevalence of 0.033% to 0.076% (Sun et al., 2021; Yao et al., 2013), while in Indonesia, the incidence rate was found to be 0.19% in a single-center study (Meylani et al., 2011). Despite the declining incidence of acute postoperative endophthalmitis, its potential to cause lasting visual impairment remains a concern, with studies showing that less than half of patients achieve satisfactory visual outcomes post-treatment (Althiabi et al., 2022).

The causative agents of acute postoperative endophthalmitis are primarily bacterial pathogens such as *Staphylococcus aureus*, Streptococcus species, and Enterococcus faecalis (Kishimoto et al., 2022; Pathengay et al., 2012; Rapuano et al., 2022). In Indonesia, *Staphylococcus aureus* was identified as the leading cause of this condition in a study conducted in Malang (Sri Agustin et al., 2020). *Staphylococcus aureus* is a gram-positive bacterium known for its role in both community-acquired and hospital-acquired infections. While typically harmless on healthy skin, it can cause severe infections once it enters tissues or the bloodstream, including endophthalmitis in ophthalmological cases (Astley et al., 2019; Taylor & Unakal, 2022).

Given the high frequency of cataract surgeries, particularly phacoemulsification procedures, stringent preventive measures are vital. These include the use of 10% povidone iodine for skin disinfection, 5% povidone iodine for the conjunctiva, and intracameral antibiotic injections post-surgery (Siahaan & Iskandar, 2015). Recent advances in preventive strategies have explored the use of bacteriophages to combat antimicrobial-resistant bacterial infections. Bacteriophages, viruses that infect and lyse bacteria, offer a promising alternative due to their bacteriolytic activity and lack of toxicity to mammalian cells (Kasman & Porter, 2021; Kishimoto et al., 2022). Studies have demonstrated the effectiveness of phage therapy in ophthalmology, including its use in treating endophthalmitis caused by Enterococcus spp. and *Staphylococcus aureus* (Fadlallah et al., 2015; Kishimoto et al., 2019). Further research into the immunological mechanisms involved in endophthalmitis, particularly the roles of myeloperoxidase (MPO) and Intercellular Adhesion Molecule-1 (ICAM-1), has been crucial in understanding disease progression and potential therapeutic targets. MPO, an enzyme produced by neutrophils, contributes to bacterial killing in the early stages of infection (Aratani, 2018; Chen et al., 2020), while ICAM-1 facilitates the migration of inflammatory cells into infected tissues, playing a key role in ocular inflammation (Bui et al., 2020; Giese et al., 2003). These insights could aid in developing novel therapeutic approaches for preventing or treating acute postoperative endophthalmitis.

Materials and Methods

Study Design

This study employed an experimental randomized posttest-only control group design. The experiment utilized New Zealand white rabbits (Oryctolagus cuniculus), which were subjected to extracapsular lens extraction surgery followed by intracameral bacterial injection to induce acute postoperative endophthalmitis. The treatment involved the injection of bacteriophages compatible with the bacteria used, specifically *Staphylococcus aureus*, a common pathogen associated with postoperative infections. This study aimed to evaluate the therapeutic effects of bacteriophage treatment on *Staphylococcus aureus*-induced endophthalmitis in a rabbit model following cataract extraction. The investigation was carried out at the Veterinary Hospital and Faculty of Veterinary Medicine, Airlangga University, Surabaya, in September 2023. The research protocol involved a comparative study between a control and a treatment group, with results evaluated using ELISA to measure ICAM-1 and MPO expression levels.

Experimental Animals

Twelve New Zealand white rabbits (Oryctolagus cuniculus), aged 4 to 10 months and weighing 2000–3000 grams, were selected for this study. These rabbits were obtained from the Veterinary Hospital of Airlangga University, Surabaya, and were housed under standard laboratory conditions. They were provided food in the form of pellets and mineral water, with care taken to maintain health and prevent pre-existing ocular conditions. A total of 12 adult New Zealand white rabbits (*Oryctolagus cuniculus*), aged between 4 to 10 months and weighing between 2,000 to 3,000 grams, were selected for this study. All rabbits were healthy with no pre-existing ocular conditions. The rabbits were randomly assigned to two groups: control (n = 5) and treatment (n = 5). Ethical approval for the use of these animals was obtained prior to the study.

Bacterial Strain and Bacteriophage

The bacterial strain used was *Staphylococcus aureus* (ATCC2297), obtained from the Microbiology Department of RSUD Dr. Soetomo, Surabaya. The bacteriophages used were specifically compatible with *Staphylococcus aureus* and were administered intracamerally after bacterial inoculation in the treatment group. To create a model of bacterial endophthalmitis, rabbits underwent extracapsular lens extraction (ECCE) surgery, followed by an intracameral injection of *Staphylococcus aureus* (strain ATCC2297, 2 × 10^5 CFU) into the anterior chamber. In the treatment group, this procedure was followed by an additional intracameral injection of bacteriophage (2 × 10^5 PFU) targeting *Staphylococcus aureus*. Both groups received postoperative antibiotic treatment with Levofloxacin eye drops to prevent secondary infection.

Animal Grouping and Procedures

The rabbits were randomly assigned into two groups. The control group received an intracameral injection of *Staphylococcus aureus*

following lens extraction surgery, while the treatment group received the same bacterial injection followed by a bacteriophage injection. Both groups underwent the same extracapsular lens extraction procedure. The periocular area was disinfected with 10% Povidone-iodine (PVI), followed by 5% PVI before making a corneal incision and performing an anterior capsulotomy using the Continuous Curvilinear Capsulorhexis (CCC) technique. The surgical site was then sutured, and Levofloxacin antibiotic eye drops were administered postoperatively to prevent secondary infections. Prior to surgery, the anterior segment of the rabbits' right eyes was evaluated using a handheld slit lamp to confirm normal ocular conditions. For preoperative preparation, the pupils were dilated using tropicamide 1% and phenylephrine hydrochloride 1%. General anesthesia was induced through an intramuscular injection of ketamine hydrochloride (35 mg/kg) and xylazine (5 mg/kg).

Extracapsular cataract extraction was performed under aseptic conditions. The periocular area was sterilized with 10% povidone-iodine (PVI), and a sterile eyelid speculum was applied. A superior corneal incision was made, followed by anterior capsulotomy using the continuous curvilinear capsulorrhexis (CCC) technique. Lens removal was performed, and intracameral injections of *S. aureus* were administered to both groups. The control group received no further treatment, whereas the treatment group received an additional injection of bacteriophage. All corneal incisions were closed with sutures, and antibiotic eye drops were administered postoperatively.

Postoperative Observation

Rabbits were monitored for 48 hours post-surgery to assess health and recovery. No rabbits exhibited signs of distress, and all maintained stable body weight and activity levels. On the third day, ocular examination revealed corneal edema in some rabbits. At this point, enucleation of the right eyes was performed for subsequent analysis. During this period, their general health was assessed, and anterior segment examinations were performed using a handheld slit lamp to ensure the surgery had normal outcomes without complications. All animals survived through the observation period.

Sample Collection and Analysis

On the third day post-surgery, the right eye from each rabbit was enucleated for analysis. Two primary markers of inflammation, myeloperoxidase (MPO) and intercellular adhesion molecule-1 (ICAM-1), were analyzed using enzyme-linked immunosorbent assay (ELISA) on the vitreous fluid samples. The eyeball tissues underwent histopathological examination, where sections were stained with hematoxylin-eosin (HE) for structural analysis. Vitreous fluid samples were collected for measurement of MPO and ICAM-1 levels using the enzyme-linked immunosorbent assay (ELISA) method. MPO levels were measured using Bioassay Technology Laboratory reagents (catalog number EA0013Rb), and ICAM-1 levels were quantified with Bioassay Technology Laboratory reagents (catalog number E0162Rb). The vitreous fluid was analyzed for differences in these inflammatory markers between the control and treatment groups.

Histopathological Analysis

Enucleated eyes were fixed in 10% formalin, embedded in paraffin, sectioned into 2 μm thick slices, and stained with HE. Microscopic examination was performed using an Eclipse E-i microscope equipped with a DS Fi2 300 megapixel camera for capturing retinal and scleral structures. Following enucleation, the rabbit eyes were fixed in 10% formalin, embedded in paraffin, sectioned at 2 μm thickness, and stained with hematoxylin and eosin (HE) for histopathological analysis. Sections were examined under a microscope (Eclipse E-i, Nikon) and photographed using a DS Fi2 300-megapixel camera. Retinal and scleral structure integrity was evaluated, with attention to pathological changes such as retinal folds, neovascularization, and inflammatory cell infiltration.

Statistical Analysis

Data from ELISA measurements of ICAM-1 and MPO were analyzed for normality and homogeneity using the Shapiro-Wilk test and Levene's test, respectively. Independent t-tests were used to assess differences between the control and treatment groups, with significance set at $p < 0.05$. Results are presented in the form of boxplots to illustrate the distribution of ICAM-1 and MPO concentrations between the groups (Figures 3 and 4).

Results

The results of this study demonstrate significant differences between the control and treatment groups in rabbits that underwent cataract extraction followed by an intracameral injection of *Staphylococcus aureus*. The treatment group, which received an additional bacteriophage injection, showed notable differences in inflammation markers compared to the control group.

Both groups were examined for ICAM-1 and MPO expression levels in the vitreous fluid using ELISA. As shown in Table 1 and Table 2, the MPO levels were slightly elevated in the treatment group (20.2974 ng/L) compared to the control group (19.5675 ng/L), although this increase was not statistically significant ($p = 0.261$). The boxplot in Figure 3 shows the distribution of MPO concentrations, with the treatment group having a higher median level than the control group. Despite the difference, the statistical analysis confirmed that it was not significant.

In contrast, ICAM-1 expression levels revealed a more pronounced difference between the two groups. As presented in Table 3, the treatment group exhibited significantly lower ICAM-1 levels (9.01 ng/L) compared to the control group (15.49 ng/L), with the difference being statistically significant ($p < 0.001$), as illustrated in Figure 4. This reduction in ICAM-1 levels in the treatment group

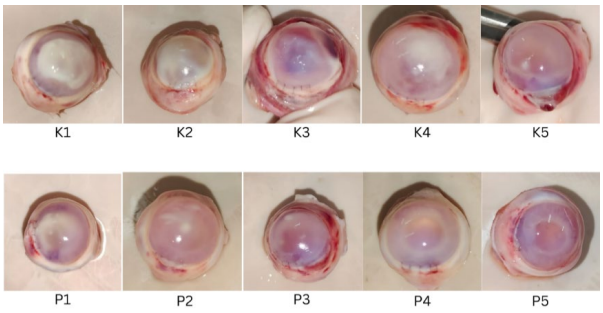

Figure 1 Comparison of eyeballs in the control group (shown in the image labeled K) and the treatment group (shown in the image labeled P).

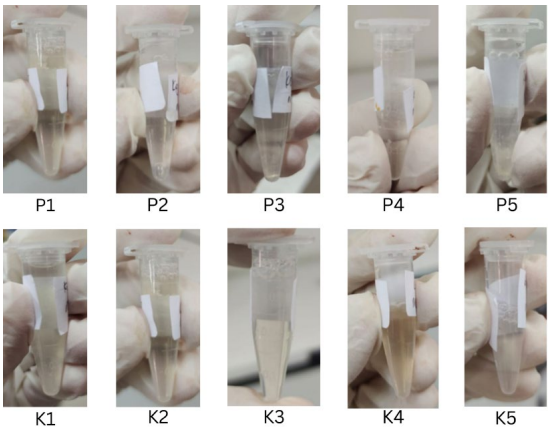

Figure 2 Vitreous fluid taken from both groups. Group P is the treatment group, and group K is the control group. In the treatment group, all the vitreous was clear. In the control group, all samples were cloudy in color

Table 1 Normality and homogeneity test between groups on MPO expression

Variable	Group	Shapiro-Wilk Normality Test	Homogeneity Test	Information
BECAUSE	Treatment Control	0,735 0,974	0,397	All groups had normal distribution, variation between groups was homogeneous

Table 2. Results of comparison of MPO concentrations between groups

Group	n	MPO level (ng/L)			p-value (one-tailed)
		Mean ± SD	Min	Max	
Treatment	5	20,2974 ± 1,3194	18,7103	22,0090	0,261
Control	5	19,5675 ± 2,0431	17,0740	22,4506	

Table 3. Normality and homogeneity test between groups on ICAM-1 expression

Variable	Group	Shapiro-Wilk Normality Test	Homogeneity Test	Information
ICAM-1	Treatment Control	0,815 0,564	0,380	All groups had normal distribution, variation between groups was homogeneous

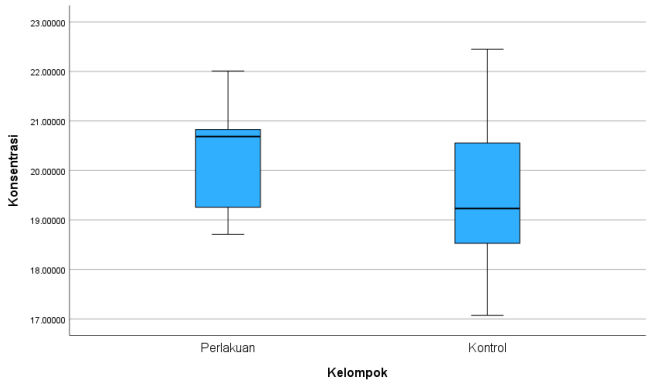

Figure 3. Diagram *boxplot* comparison of MPO concentrations between groups

Table 4. Results of comparison of ICAM-1 concentrations between groups

Group	n	ICAM-1 level (ng/L)			p-value (one-tailed)
		Mean ± SD	Min	Max	
Treatment	5	9,0104 ± 1,4753	7,3645	11,0104	<0,001
Control	5	15,4895 ± 0,9845	14,0312	16,4270	

p<0.05 = significant

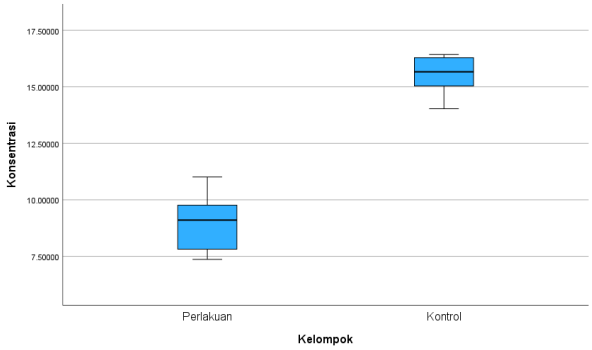

Figure 4. Boxplot diagram of comparison of ICAM-1 concentrations between groups

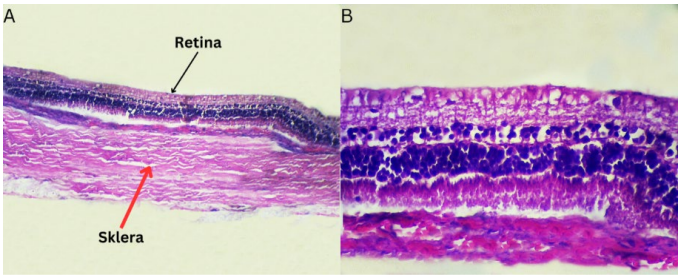

Figure 5. Image of retinal structure obtained in the treatment group. Figure A: black shows the inner layer of the retina and red arrows show the sclera. (HE staining; Image A magnification 40x, slide B 100x; Eclipse E-i microscope; DS Fi2 300 megapixel camera; bar=50μm and 100 μm).

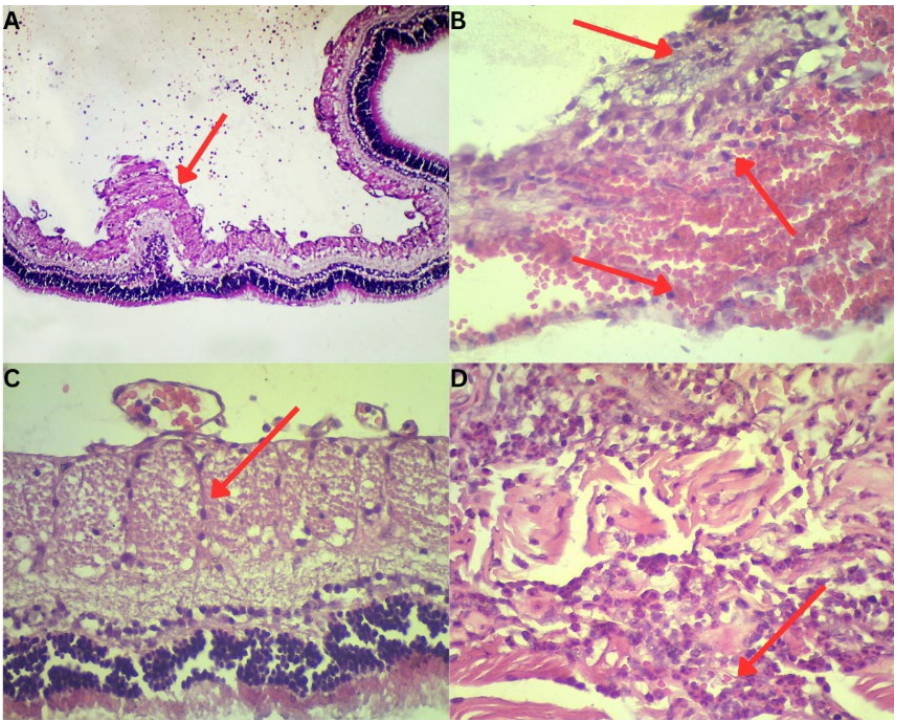

Figure 5. Pathological features of the retina, choroid and sclera in the control group. Figure A: pathological folds in the retina (shown by red arrow). Image B: Bleeding accompanied by inflammation of the inner layer of the retina. It appears that the boundary between the retina and the choroid becomes blurred. Image C: retinal neovascularization followed by neutrophil inflammatory cells (indicated by red arrows). Figure D: Infiltration of inflammatory cells by neutrophils and macrophages in the sclera (shown by red arrows), accompanied by stretching of the scleral wall and scleral neovascularization. (HE staining; slide A magnification 40x, slides B and C 100x, slide D 400x; Eclipse E-i microscope; DS Fi2 camera 300 megapixels).

Table 5. Comparison of vitreous fluid clarity between treatment and control groups.

Group	Vitreous Fluid Appearance	Inflammation Level	Neutrophil Infiltration
Treatment	Clear	Low	Minimal
Control	Cloudy	High	Extensive

suggests that bacteriophage therapy helped mitigate inflammation more effectively than the control treatment.

The histopathological examination further supported these findings. In the treatment group, retinal and scleral structures remained largely intact, as shown in Figure 5. In contrast, the control group displayed severe retinal damage, including pathological folds, detachment from the sclera, and signs of retinal neovascularization. Neutrophil infiltration and scleral neovascularization were also observed in the control group (Figure 5).

These results indicate that bacteriophage treatment reduced inflammation and preserved retinal structure compared to the control group, as evidenced by the significantly lower ICAM-1 levels and reduced tissue damage observed in the histopathological analysis. The macroscopic images in Figure 1 further illustrate the difference in inflammation, with the treatment group showing less corneal cloudiness and minimal hypopyon compared to the control group. Additionally, vitreous fluid analysis in Figure 2 confirmed that all treatment group samples were clear, whereas the control group samples were cloudy, reinforcing the treatment's effectiveness in mitigating the severity of the infection.

Discussion

Postoperative acute endophthalmitis is one of the most severe complications following cataract surgery, often leading to significant vision loss and potential blindness if not managed effectively. The primary cause of this condition is bacterial infection, predominantly by pathogens such as *Staphylococcus aureus* and *Enterococcus faecalis* (Creuzot-Garcher et al., 2016; Kumar & Kumar, 2015; O'Callaghan, 2018). Although technological advances and improved prophylactic measures have reduced the incidence of this complication, acute endophthalmitis continues to pose a serious threat due to its rapid progression and the devastating visual outcomes, even after treatment (Sun et al., 2021). Recent studies have shed light on the pathophysiological mechanisms underlying endophthalmitis, particularly emphasizing the role of bacterial virulence factors in mediating ocular inflammation and vascular damage (Jiang et al., 2022; Plumet et al., 2022). This discussion aims to explore the key findings of recent research on postoperative acute endophthalmitis, analyzing pathogen interactions, immune response, and emerging therapeutic approaches.

Pathogenesis of Bacterial Endophthalmitis

Bacterial endophthalmitis involves complex interactions between host tissues and invading pathogens. The pathogens, such as *Staphylococcus aureus* and *Bacillus cereus*, release toxins that induce a strong immune response, leading to inflammation, tissue damage, and disruption of the blood-retinal barrier. This results in the influx of immune cells, including neutrophils, into the vitreous, contributing to tissue damage through the release of pro-inflammatory mediators (Ahmad & Rehman, 2023; Hall et al., 2008).

Histological evidence from experimental models demonstrates that endophthalmitis causes extensive retinal damage, with pathologic folds, retinal detachment, and neovascularization (Omuta et al., 2007). These findings are consistent with the work of Gregory et al. (2007), who showed that bacterial invasion leads to retinal apoptosis, particularly in the ganglion and inner and outer nuclear layers. Moreover, the production of inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, is pivotal in exacerbating retinal damage (Kumar & Kumar, 2015). This highlights the rapid progression of the disease, as seen with *Bacillus cereus*, which can cause complete retinal destruction within 12 to 48 hours (Mursalin et al., 2019).

Immune Response and Tissue Damage

One of the primary drivers of tissue damage in endophthalmitis is the immune response, particularly neutrophil infiltration. Neutrophils are the first responders to bacterial infection, releasing myeloperoxidase (MPO), proteases, and reactive oxygen species that aim to eliminate pathogens but also inadvertently damage host tissues (Aratani, 2018; Andrés et al., 2022). Elevated MPO levels in vitreous fluid have been correlated with severe inflammation and tissue destruction in bacterial endophthalmitis (Sanders et al., 2013).

In our study, vitreous samples from the control group, which exhibited severe endophthalmitis, showed cloudy vitreous fluid with a high degree of neutrophil infiltration, consistent with increased MPO levels (Figure 1). In contrast, the treatment group had clearer vitreous fluid and reduced inflammatory infiltration, indicating the efficacy of the therapeutic intervention. This aligns with previous findings that highlight the importance of MPO as a biomarker of inflammation in endophthalmitis (Kishimoto et al., 2019).

Role of Myeloperoxidase in Endophthalmitis

MPO, a crucial enzyme in neutrophils, catalyzes the production of hypochlorous acid, a potent antimicrobial agent (Andrés et al., 2022; Malle et al., 2007). While MPO plays a critical role in controlling infections, its excessive production in response to severe infections like endophthalmitis leads to oxidative stress and subsequent tissue damage (Schindhelm et al., 2009). In bacterial endophthalmitis, elevated MPO levels indicate the degree of neutrophil activity, serving as a marker for both infection severity and treatment outcomes (Ali et al., 2016). The increased MPO levels observed in the treatment group may reflect the effectiveness of bacteriophage therapy in reducing bacterial load and subsequent neutrophil recruitment (Das et al., 2021).

However, the non-significant difference in MPO levels between the treatment and control groups in this study suggests that extracapsular lens extraction, which induces more significant

inflammation than phacoemulsification (PE), might have contributed to the increased MPO levels (Khanday et al., 2015; Laurell et al., 1998). PE is associated with a lower inflammatory response due to its smaller incision size and reduced manipulation of ocular structures (Chee et al., 1999).

ICAM-1 and Leukocyte Recruitment

ICAM-1 (Intercellular Adhesion Molecule-1) is a critical transmembrane glycoprotein that facilitates leukocyte adhesion and transmigration during inflammation. Its expression is upregulated in response to pro-inflammatory cytokines, playing a significant role in leukocyte infiltration during endophthalmitis (Haydinger et al., 2023). Studies have shown that ICAM-1 expression peaks during the early stages of infection and is associated with maximum leukocyte infiltration (Coburn et al., 2015).

In our study, ICAM-1 levels in the vitreous fluid were significantly lower in the treatment group compared to the control group, indicating that the therapeutic intervention effectively reduced leukocyte infiltration and inflammation (Bui et al., 2020) (Table 4, Table 5). The lower ICAM-1 levels suggest a reduced inflammatory response, aligning with studies demonstrating decreased ICAM-1 expression following successful treatment of eye infections (Berger et al., 2002; Hadar et al., 2005).

Emerging Therapies: Bacteriophage Therapy

Given the growing concern over antibiotic resistance, alternative treatment modalities, such as bacteriophage therapy, have gained traction. Bacteriophages are viruses that specifically target bacterial cells, offering a highly specific and potentially effective treatment for multidrug-resistant bacterial infections (Deshmukh et al., 2018; Fadlallah et al., 2015). Bacteriophage therapy has shown promise in the treatment of refractory bacterial keratitis and endophthalmitis, with studies demonstrating its effectiveness in reducing bacterial load without affecting beneficial ocular microbiota (Miller et al., 2019).

Bacteriophage therapy offers a targeted approach to bacterial infections by selectively lysing pathogenic bacteria while sparing host tissues and normal flora (Pina et al., 2022). In this study, the treatment group receiving bacteriophage therapy showed significantly lower levels of retinal damage and inflammatory cell infiltration compared to the control group. These findings support the growing body of evidence suggesting that bacteriophages could serve as a viable alternative to traditional antibiotics in treating ocular infections (Sybesma et al., 2016).

Prophylactic Strategies

Prophylactic measures, such as intracameral antibiotic injections, have become a cornerstone in preventing postoperative endophthalmitis. Studies show that antibiotics such as vancomycin, cefuroxime, and moxifloxacin significantly reduce the risk of infection when administered at the time of surgery (Sen et al., 2023). However, the rising incidence of antibiotic-resistant bacteria has prompted researchers to explore alternatives, such as bacteriophage therapy, for prophylaxis (Wittebole et al., 2014).

Bacteriophages can be tailored to target specific bacterial strains, providing a highly specific prophylactic measure against endophthalmitis (Zhang & Cheng, 2022). Moreover, their ability to minimize collateral damage to beneficial ocular microbiota makes them an attractive option for infection prevention.

Conclusion

Postoperative acute endophthalmitis remains a significant challenge in ophthalmic surgery, despite advances in prophylactic and therapeutic measures. The rapid progression of the disease and the severe visual impairment it causes underscore the need for effective treatments. The findings of this study demonstrate the potential of bacteriophage therapy as an emerging treatment modality, offering a targeted and sustainable alternative to antibiotics. Additionally, the role of immune markers such as MPO and ICAM-1 in the progression of endophthalmitis highlights their utility as biomarkers for disease severity and treatment outcomes. Future research should focus on optimizing bacteriophage formulations and delivery methods, as well as exploring their potential for prophylaxis in high-risk surgical patients.

Author contributions

M.I.M.I.H. conceptualized the study and designed the methodology. I.Z., R.L., and W.S. contributed to data collection and analysis. L.A. and D.I. were involved in data interpretation and manuscript drafting. F.S., A.P., and D.L. provided critical revisions and supervised the overall research process. All authors reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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