

# Electroretinographic Evaluations Using Skin Electrode of Eyes with Bleb-Related Endophthalmitis Following Vitrectomy with 0.025% Povidone Iodine Irrigation

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**Purpose:** To determine whether 0.025% povidone-iodine (0.025% PI) in the irrigation solution during vitrectomy for endophthalmitis is safe.

**Methods:** Two cases of bleb-associated endophthalmitis were treated with vitrectomy using 0.025% PI in the irrigation solution. The RETeval electroretinographic (ERG) system with skin electrodes was used to assess the physiology of the retina pre- and postoperatively.

**Case:** Case 1 was a 46-year-old man who had atopic keratoconjunctivitis and underwent trabeculectomy with the creation of a bleb after there was a rise in the intraocular pressure. One month postoperatively, a mild filtering bleb-associated endophthalmitis developed, and the eye was treated with intravitreal and subconjunctival injections of vancomycin (VCM) and ceftazidime (CAZ). After three days, the fundus was not visible and B-mode echography showed an area of high brightness in the retina. Vitrectomy with irrigation with VCM and CAZ, and 0.025% PI was performed successfully. Pre- and postoperative ERGs showed an improvement in both the a- and b-wave amplitudes and the b/a ratio was stable at 2.0. Case 2 was a 63-year-old man who had undergone trabeculectomy for glaucoma. Five years later, the eye developed blebitis which was treated with topical and subconjunctival injections of VCM and CAZ. Three days later, vitreous opacities appeared and a high brightness area was seen in the B-mode echographic images. Vitrectomy with VCM and CAZ, and 0.025% PI irrigation was successfully performed. Comparisons of the pre- and postoperative ERGs found that the a- and b- wave amplitudes of the ERGs increased and the b/a ratio was stable at approximately 1.5.

**Conclusion:** Vitrectomy with 0.025% PI irrigation is safe and ERG recordings with skin electrodes can be used to evaluate the pre- and postoperative retinal physiology safely.

**Plain Language Summary:** We report our findings in two cases of bleb-related endophthalmitis that underwent pars plana vitrectomy (PPV) with irrigation with 0.025% povidone-iodine (PI)-Balanced Salt Solution (BSS) PLUS (Alcon Laboratories, Fort Worth, TX). The retinal function was evaluated by full-field electroretinograms (ERGs) recorded with skin electrodes before and after the vitrectomy.

At present, there is no consensus on whether patients with bleb-related endophthalmitis should be treated with PPV or treated solely by intravitreal antibiotics. It was recently reported that vitrectomy using an irrigation solution containing 0.025% PI followed by postoperative antibiotics was effective and safe for the treatment of endogenous endophthalmitis and postoperative endophthalmitis. However, iodine is known to be retinotoxic depending on its concentration.

Electroretinography is a useful method to evaluate the safety of medications because it represents the physiology of the entire retina. However, conventional recording procedures with contact lens electrodes cannot be used in eyes with bleb associated endophthalmitis. Therefore, we performed ERG using skin electrodes which were introduced relatively recently. As a result, electroretinographic response showed that retinal function was not altered after surgery in these two cases.

**Keywords:** blebitis, electroretinography, bleb-related endophthalmitis, povidone iodine irrigation, vitrectomy

## Introduction

Bleb-related endophthalmitis is a severe complication that can develop after mitomycin C-augmented trabeculectomy or trabeculectomy alone.<sup>1,2</sup> The endophthalmitis develops at a mean time of  $6.9 \pm 5.8$  years after the surgery, and the 5-year cumulative incidence is  $2.2 \pm 0.5\%$ . This incidence is higher than that of infections after cataract surgery.<sup>1</sup> The infections are classified into: Stage I or blebitis confined to the bleb site with a mild cellular reaction in the anterior chamber, Stage II infections affect mainly the anterior chamber and the vitreous is not involved, and Stage III infections affect the posterior segment of the eye. Stage III is subdivided into IIIa with mild involvement of the vitreous and Stage IIIb with more advanced involvement of the vitreous.

The inflammation of Stage III blebs spreads into the vitreous within 12 months in 31.5% (46/146) of the eyes and causes a significant decrease in vision and elevation of the intraocular pressure (IOP).<sup>3</sup> Repeated intravitreal injections of antibiotics for Stage IIIa, and immediate vitreous surgery for Stage IIIb are recommended. In addition to the surgical removal of the infected vitreous, topical and intravitreal vancomycin (VCM) and ceftazidime (CAZ) are used as first-line treatments because they have broad-spectrum antibacterial activity with a low potential for developing resistance.<sup>4</sup>

Recently, Nakashizuka et al reported a safe and effective adjunct to vitrectomy using an irrigation solution containing 0.025% povidone-iodine (PI) followed by postoperative antibiotics for the treatment of exogenous or endogenous endophthalmitis including blebitis-related endophthalmitis.<sup>5–7</sup> However, there are several reports on the toxicity of PI on the retina,<sup>8–11</sup> and only limited information is available on its safety in human eyes with severe endophthalmitis.<sup>6,7</sup>

Electroretinography (ERG) has been used to assess the physiology of the retina objectively,<sup>6</sup> however the contact lens electrodes used to pick-up the ERGs can have an adverse effect on the filtering bleb. This is because the contact lens electrode is larger than the cornea and can make physical contact with the filtering bleb. Although a wire electrode such as the DTL electrode can be used for eyes with a filtering bleb, it is not available in all clinics. To overcome this difficulty, skin electrodes are used to record the ERGs without affecting the filtering bleb and avoid exposing infectious microorganisms to the bleb.<sup>12</sup>

The purpose of this report is to present our findings in two cases of extraneous endophthalmitis that were treated with pars plana vitrectomy (PPV) with irrigation of 0.025% PI diluted in balanced salt solution (BSS) PLUS (Alcon Laboratories, Fort Worth, TX). The status of the retinal physiology was determined by full-field ERGs that were recorded with the RETeval system and skin electrodes before and after the vitrectomy.

The procedures used on these patients were approved by the Ethics Committee of Saitama Medical University (No.2021–073), and the study was conducted in accordance with the tenets of the Declaration of Helsinki. A signed written informed consent was obtained from the two patients who participated in this study. The consent form included a statement that the patients allowed the treating physicians to publish the findings and any accompanying images published anonymously. Institutional approval was waived because of the retrospective design of this study.

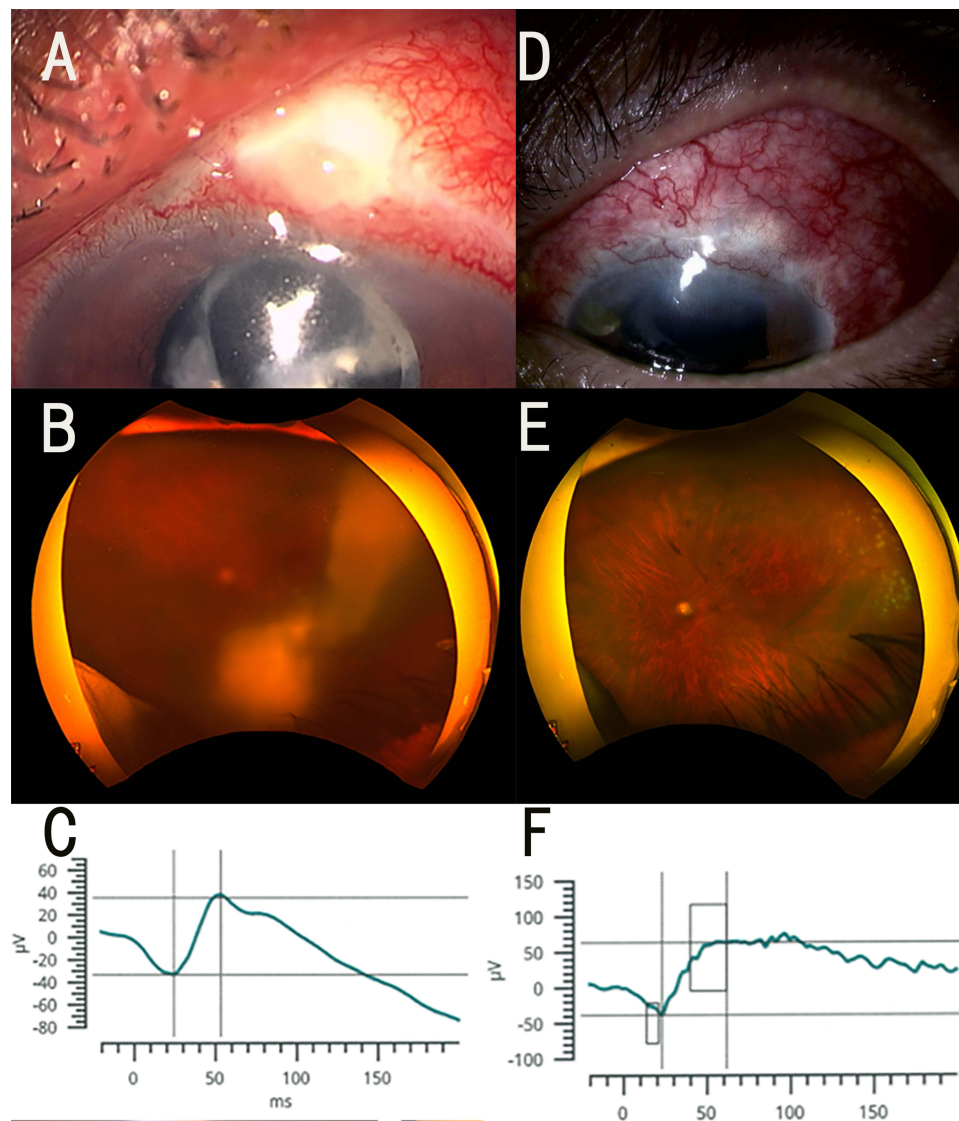
## Case Reports

Case 1 was a 46-year-old man who complained of ocular pain in his left eye in July of 202X. His decimal best-corrected visual acuity (BCVA) in the left eye was 0.2 and the IOP was 23.9 mmHg. He had been diagnosed with atopic keratoconjunctivitis and steroid-induced glaucoma in his left eye. Trabeculectomy had been performed one month before our examination.

Our slit-lamp examination showed conjunctival hyperemia, mild opacity of the superior cornea, and cells and mild flare in the anterior chamber (Figure 1). The opacification in the anterior vitreous was mild, but the visibility of the fundus was poor. Clear optical coherence tomographic (OCT) images were not available.

A mild, filter bleb-associated endophthalmitis was suspected and he was treated by subconjunctival injections of 5 mg/0.5 mL of VCM (Meiji Seika Pharma Co., Ltd., Tokyo, Japan,) and 10 mg/0.5 mL of CAZ (Viatris Global Healthcare Company, PIT, PA). He was also treated with intravitreal injections of 1.0 mg/0.1 mL VCM and 2.0 mg/0.1 mL CAZ, and frequent topical antibiotics. Examinations of the cultures of the secretions around the bleb were negative.

Three days later, his BCVA decreased to hand movements, and the fundus was not visible ophthalmoscopically. B-mode echography showed a high brightness area. He was diagnosed with a Stage IIIb endophthalmitis, and he was



**Figure 1** Case 1. This patient developed exogenous endophthalmitis after undergoing trabeculectomy. Slit-lamp images, fundus photographs, optical coherence tomographic (OCT) images, and electroretinograms (ERGs) before and during the bleb-associated endophthalmitis are shown. (A) Slit-lamp image on the initial visit showing an avascular bleb, conjunctival hyperemia, and a mild upper corneal opacity. (B) Fundus photograph 1 day before the surgery showing that the fundus was not visible due to vitreous opacity. (C) Mixed rod-cone electroretinogram (ERG) on the initial visit. The a- and b- wave amplitudes are moderately attenuated. (D) Slit-lamp image 2 weeks after surgery showing reduced height of the avascular bleb and slightly decreased injection. (E) Fundus photograph 4 days after surgery showing an intact retinal circulation and pale optic disc. (F) Mixed rod-cone ERG 3 days after the surgery. The a- and b-wave amplitude is larger than the preoperative values, and the b/a ratio is not changed at approximately 2.0 postoperatively. The implicit time of both waves was not altered. Note that the vertical axis representing the amplitude has a different scale.

treated with vitrectomy with 10 mg/500 mL VCM, 20 mg/500 mL CAZ, and 0.025% PI irrigation. Immediately before the start of surgery, 0.025% PI was prepared by adding 1.25 mL of 10% PI to 500 mL of BSS Plus. This solution was used for a two-port anterior chamber irrigation and also during vitrectomy. Before starting the vitrectomy and after mixing a new bottle of PI-BSS PLUS, the infusion cannula was left open to drain out approximately 50 mL of the older PI-BSS PLUS solution. This was done because it was expected that nearly 50 mL of the previous solution would remain in the vitrectomy device. At the beginning of the surgery, the irrigation was paused to take samples from the vitreous cavity for culture. The vitreous cavity was irrigated with the solution for 15 minutes, and thereafter the anterior chamber was washed with a new bottle of 0.025% PI-BSS PLUS. This is because the effectiveness of this solution against pathogens is limited to less than 15 minutes.<sup>5</sup> The amount of the solution used was approximately 200 mL. The surgeon determined whether to leave or remove the avascular bleb. We suggest that the bleb was also cleansed by the anterior

chamber irrigation. Then, 1.0 mg/0.1 mL of VCM and 2.0 mg/0.1 mL of CAZ were injected intravitreally at the end of the vitrectomy.

No causative microorganisms were detected in the cultures of the eye discharges around the bleb collected preoperatively, in the preoperative aqueous humor, or in the intraocular fluid obtained by intraoperative vitreous biopsy. One month after the surgery, the visual acuity improved to counting fingers. Thereafter, neither intraocular inflammation nor corneal decompensation was observed, and the IOP remained controlled under 15 mmHg in the glaucomatous eye for 2 years. Specular microscopy showed that the endothelial cell density was 2351 /mm<sup>2</sup> before surgery and 2232 /mm<sup>2</sup> at the last examination. The patient is being followed to determine any long term adverse events.

Full-field ERGs were recorded 3 days before the surgery and 3 days after the surgery with the RETeval system (LKC Technologies, Gaithersburg, MD; Welch Allyn, Skaneateles Falls, New York, USA), a portable ERG system that uses skin electrodes. The recording conditions of the RETeval system conform to the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV).<sup>13</sup> The RETeval system picks up the ERGs with a skin electrode array (Sensor Strip; LKC Technologies, Inc.) that is placed on the skin 2 mm from the margin of the lower eyelid.<sup>14</sup> This electrode array contains the active, reference, and ground in a single adhesive tape. The electrical potentials are DC-amplified and digitized at a 2 kHz sampling rate. The data resolution is 24 bits for ±0.6 V which is equal to approximately 0.07 μV. Comparisons of the pre- and postoperative ERGs showed an improvement of the a- and b-wave amplitudes and a stable b/a ratio of approximately 2.0 (Figure 1). The implicit times of both waves did not change significantly.

Case 2 was a 63-year-old man who complained of pain in his left eye in March 202X. His BCVA in the left eye was hand movements, and the IOP was 15.0 mmHg. He had undergone combined cataract and vitreous surgery for proliferative diabetic retinopathy (PDR) 11 years earlier and trabeculectomy for glaucoma of the left eye 5 years earlier.

Slit-lamp examination showed conjunctival hyperemia with cells and moderate flare in the anterior chamber (Figure 2). Ophthalmoscopy showed mild vitreous opacity, and the OCT image was not clear but the retina could be seen to be atrophic probably due to the proliferative diabetic retinopathy PDR. A bleb-associated endophthalmitis (Stage IIIa) was suspected.

He was treated with intravitreal injections of 1 mg/0.1 mL of VCM and 2 mg/0.1 mL of CAZ and subconjunctival injections of 1 mg/0.1 mL of VCM and 2 mg/0.1 mL of CAZ. *Haemophilus influenzae* was detected in the cultures of the secretions around the bleb, and drug sensitivity tests showed that the *H. influenzae* was sensitive to levofloxacin and VCM, and resistant to Ampicillin. The sensitivity to CAZ was not determined. Three days later, the vitreous opacity worsened, and a high brightness area was observed in the B-mode echographic images. A diagnosis of bleb-associated endophthalmitis (Stage IIIb) was made, and PPV with 1 mg/0.1 mL of VCM, 2 mg/0.1 mL of CAZ, and 0.025% PI irrigation was performed in the same way as Case 1. The visual acuity recovered to 0.01 one month after the beginning of the treatments. Thereafter, neither the intraocular inflammation nor the corneal decompensation occurred, and the IOP was controlled under 15 mmHg with topical glaucoma medications for more than 2 years. Specular microscope showed that the preoperative endothelial cell density was 1378 /mm<sup>2</sup> and it was 1094 /mm<sup>2</sup> at the last visit.

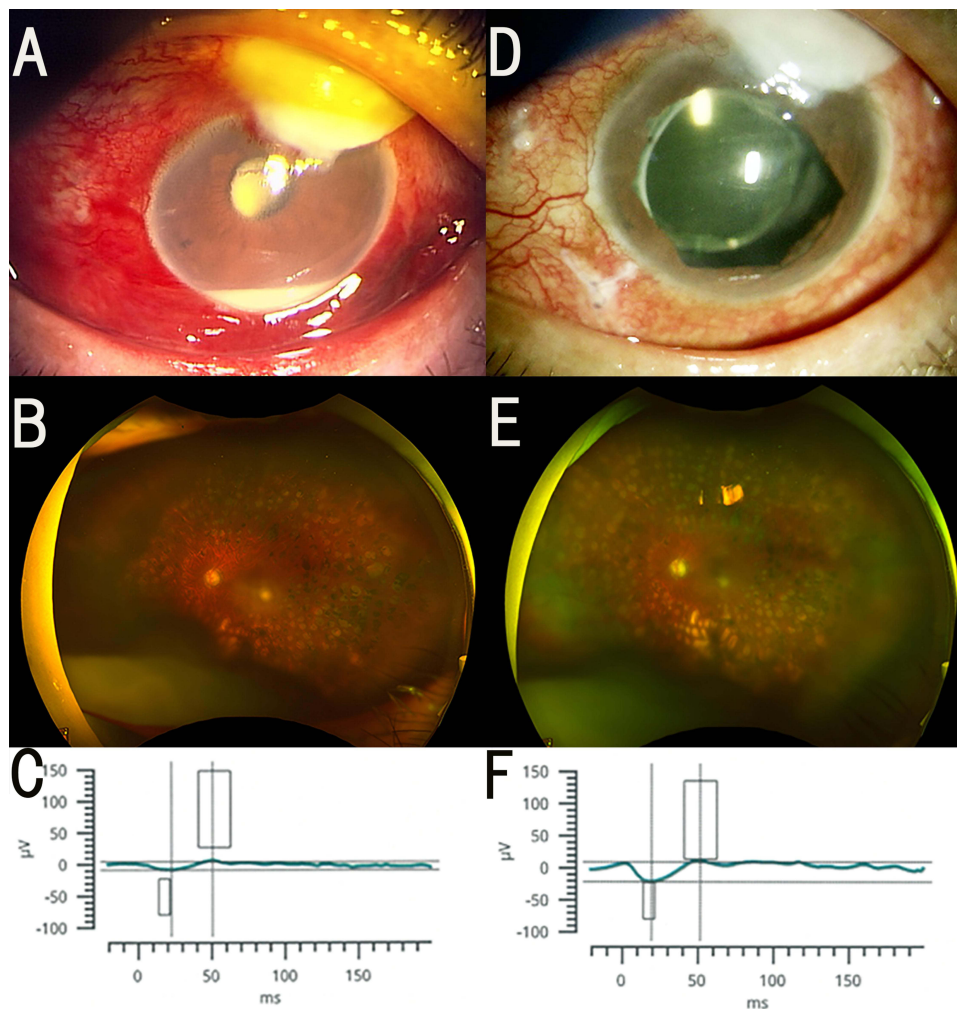
Full-field ERGs were recorded 3 days before the surgery and 6 days after the surgery with the RETeval system. Comparisons of the pre- and postoperative ERGs showed that the a- and b- wave amplitudes increased but the b/a ratio was not significantly changed at approximately 1.5 months postoperatively. The implicit times of both waves was also not significantly changed (Figure 2).

## Discussion

The microorganisms responsible for the bleb-associated endophthalmitis can be identified in cultures but about 50% of these cases are culture-negative. When identified, the most frequent organisms are members of the *Staphylococci* and *Streptococci* genus.<sup>2,3</sup>

PI acts directly on the membrane proteins of bacteria and viruses to inactivate them, and thus acts with or without drug resistance. The time for antimicrobial action is as short as 15 seconds at a 0.025% concentration.<sup>5</sup> In Stage IIIb filtering bleb-related infections, *H. influenzae* and *Enterococcus* species have also been detected.<sup>3</sup> There is also a report that VCM-resistant *enterococci* were determined to be causative pathogen of filtering bleb-related endophthalmitis.<sup>15</sup> Our results showed that 0.025% PI irrigation in combination with antimicrobial perfusion was effective in treating the current





**Figure 2** Case 2. Slit-lamp images, fundus photographs, optical coherence tomographic (OCT) images, and electroretinograms (ERGs) before and during the course of the bleb-associated endophthalmitis. **(A)** Slit-lamp image on the initial visit showing an avascular bleb, conjunctival hyperemia, and mild upper corneal opacity. **(B)** Fundus photograph 2 day before surgery showing relatively intact fundus before the exacerbation of an endophthalmitis. The fundus photograph was not taken due to opacified media on the following day. **(C)** Mixed rod-cone ERG on the initial visit. The a- and b- wave amplitudes are markedly reduced. **(D)** Slit-lamp image 2 weeks after the vitrectomy with irrigation containing 0.025% povidone iodine. Image shows white avascular bleb and decreased injection. **(E)** Fundus photograph 4 days after surgery showing an intact retinal circulation and pale optic disc. **(F)** Mixed rod-cone ERG 6 days after surgery. Compared to the preoperative response, the a- and b-wave amplitudes are larger, and the b/a ratio has not changed at approximately 1.5. The implicit times of both waves are not significantly changed.

cases. Because PI acts directly on the membrane proteins of bacteria and viruses to inactivate them, it has a low possibility for the microorganisms to become resistant to the drug. Another advantage of PI is the rapidity of its action.

However, iodine is reported to be retinotoxic depending on its concentration which raises the possibility of retinal toxicity with its use.<sup>8–11</sup> In experiments on rabbits, PI at concentrations of 0.027% or lower had no histological effects on the intraocular tissues.<sup>9</sup> Intravitreal administration of 0.1 mL of 1.25% PI and irrigation of the vitreous cavity with 0.025% PI for 15 minutes for endophthalmitis showed no alteration of the retinal physiology of the postoperative ERGs.<sup>6</sup> In addition, there is only one report of two cases that used 0.025% PI combined with antibiotics in the irrigation solution during vitrectomy for filtering bleb-associated endophthalmitis.<sup>7</sup> Unfortunately, the authors did not perform ERG recordings. In our two cases, there was no postoperative reduction of retinal physiology as shown by the ERGs as reported earlier.

The prognosis of endophthalmitis has been evaluated by the visual acuity in earlier studies.<sup>2,6,7,16–19</sup> Although perimetry and ERGs are helpful in assessing the physiology of the entire retina, there are only a small number of studies using these methods probably because of their longer testing times which can be inconvenient for the patients.<sup>6,20</sup>

The RETeval system is a relatively new ERG recording system that uses skin electrodes and is less invasive.<sup>21</sup> We showed that the ERGs recorded with skin electrode can be used to evaluate the retinal physiology in the early postoperative period even in eyes after filtration surgery in which contact lenses and DTL electrodes cannot be used.<sup>12,22,23</sup>

Dense opacities, such as that caused by hemorrhage, mature cataracts, or thick fibrous membranes, can reduce the ERG responses. So the effects of media opacities should be considered when comparing the ERGs in some cases.<sup>24–27</sup> Fortunately, in our cases, preoperative ERG recordings were made before fundus visibility significantly deteriorated, and postoperative ERG recordings were performed after the fundus visibility had recovered. So the effects of media opacities were minimal. When comparing ERGs before and after the vitrectomy, it should be remembered that the postoperative ERGs are affected by retinal damage due to endophthalmitis, surgical invasion, and drugs used during surgery. Taking these into consideration, the fact that the response was not significantly reduced suggests that there was relatively little iatrogenic retinal damage and that the treatment was effective.

These were only two cases, and the safety and effectiveness of this treatment cannot be applied to all cases because there are many factors that affect the prognosis of endophthalmitis. However, the relatively long follow-up period without intraocular inflammation and corneal decompensation suggests that the antibiotics and PI used during surgery had minimal adverse effects on the retina and cornea. It is necessary to investigate a larger number of cases for a longer follow-up times to determine whether a recurrence of endophthalmitis can be prevented by this method. Nevertheless, we believe that these findings will contribute to the establishment of a treatment protocol for bleb-associated endophthalmitis and maybe other forms of endophthalmitis.

In conclusion, vitrectomy with 0.025% PI irrigation is a safe and effective method to treat bleb-associated endophthalmitis. However, a complete absence of retinal toxicity was not proven. ERG recordings with skin electrodes can be used to evaluate the perioperative retinal function of bleb-associated endophthalmitis.

## Study Approval Statement

The study was conducted according to the guidelines of the Declaration of Helsinki. The vitrectomy using 0.025% povidone-iodine in irrigation solution for bleb-related endophthalmitis was approved by the Ethical Committee of Saitama Medical University (2021-073).

## Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## Consent to Publish Statement

Written informed consent was obtained from participants after full explanation of the diagnosis and treatment. Institutional approval was waived because of the retrospective design of this study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors have no conflicts of interest to declare in this work.

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