tvst

https://doi.org/10.1167/tvst.8.1.21

Article

Intravitreal Injection of 1.25% Povidone Iodine Followed by Vitrectomy Using 0.025% Povidone Iodine Irrigation for Treating Endophthalmitis

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Received: 25 October 2018
Accepted: 10 December 2018
Published: 13 February 2019

Keywords: povidone iodine; intravitreal injection; endophthalmitis; vitrectomy; electroretinogram

Citation: Nakashizuka H, Shimada H, Hattori T, Tanaka K, Kitagawa Y, Shinoda K. Intravitreal injection of 1.25% povidone iodine followed by vitrectomy using 0.025% povidone iodine irrigation for treating endophthalmitis. Trans Vis Sci Tech. 2019;8(1):21, https://doi.org/10.1167/tvst.8.1.21

Purpose: To investigate the safety and effectiveness of intravitreal injection (IVI) of 1.25% povidone iodine (PI) followed by vitrectomy using 0.025% PI irrigation for treating endophthalmitis.

Methods: Prospective case series study. Nine eyes of 8 patients with postoperative or endogenous endophthalmitis treated at the Nihon University Hospital between April 2015 and October 2017 were studied. First, IVI of 0.1 mL/1.25%PI was conducted, followed by anterior chamber irrigation and vitrectomy using 0.025%PI irrigation solution. Corneal epithelial damage, anterior chamber inflammation, and vitreous inflammation were assessed and fundus examinations were performed, using a slit-lamp microscope and indirect ophthalmoscopy. A specular microscope, Goldmann perimetry, and electroretinography (ERG) were also used.

Results: In all but case 7, endophthalmitis resolved rapidly and good visual acuity was maintained. No adverse events were noted. Furthermore, the perioperative ERG showed improvements in the oscillatory potentials amplitudes on ERG and flicker ERG, as well as in the implicit time of the a-wave, suggesting functional recovery in the retinal outer and inner layers after therapy.

Conclusions: IVI of PI followed by vitrectomy was thought to be a safe and effective treatment for endophthalmitis.

Translational Relevance: We succeeded in proving the clinical safety of IVI of PI followed by vitrectomy with PI irrigation as well as previous experimental reports. PI is available in world widely, therefore this method will be optimal treatment for endophthalmitis.

Introduction

Endophthalmitis is the one of the most devastating complications of ocular surgeries resulting in poor visual outcomes. Povidone iodine (PI) is the only preoperative disinfectant, which has received the intermediate clinical recommendation (B, moderately important to clinical outcome).[1] As to bacterial endophthalmitis prophylaxis in cataract surgery, the recent literature strongly supports the use of preoperative PI antisepsis.[2] PI exhibits a wide range of microbicidal actions against multidrug-resistant bacteria,[3] Candida,[4] viruses,[5] and acanthamoeba,[6] and is also active against biofilms.[7] PI has the additional advantages of low cost, the absence of drug resistance, and a rapid bactericidal effect as compared with antibiotics.[8]

We have also reported repeated irrigation of the operative field with 0.25% PI to be safe for ocular tissues and highly bactericidal in a wide range of ocular surgeries, including cataract operations,[9] vitrectomy,[10] and buckling procedures.[11]

Furthermore, we previously reported that 0.025%PI-Balanced Salt Solution (BSS) PLUS (Alcon

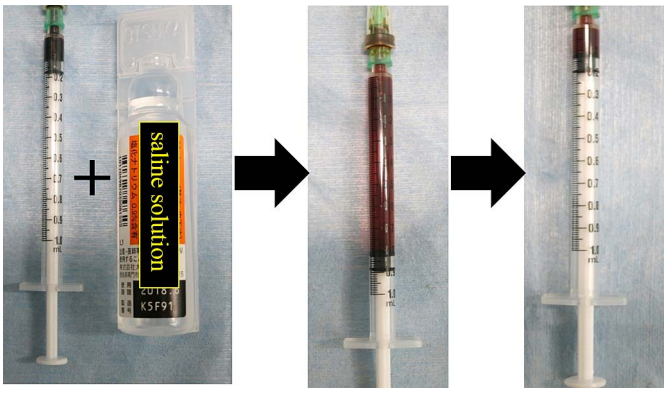

Figure 1. How to make 1.25%/0.1 mL of PI. First, 0.1 mL of 10%PI, which is an undiluted solution of PI, is taken into a 1-mL syringe. The needle is then exchanged for a new one, and 0.7 mL of saline solution is added, resulting in 0.8 mL of the solution. The solution is mixed well to achieve a uniform concertation. This is further reduced to 0.1 mL (i.e., to a 0.1-mL volume of 1.25%PI) which is administered by IVI using a 30-G needle.

Laboratories, Fort Worth, TX) is bactericidal and nontoxic when used as an irrigation solution for vitrectomy in eyes with endophthalmitis.[12] This therapy for endophthalmitis is anticipated to become a new treatment for endophthalmitis caused by multidrug-resistant organisms, such as vancomycin-resistant bacteria and fungal organisms.

In fact, however, bacterial growth kinetics revealed that *Enterococcus faecalis* increases by a factor of 100 in only 7 hours[13] and *Candida albicans* increases in 24 hours.[14] Considering these kinetics, initial treatment for endophthalmitis is the most important step in preventing bacterial growth. We devised a plan that involves intravitreal injection (IVI) of PI as an initial treatment for endophthalmitis. We herein report the clinical effectiveness of IVI of PI followed by vitrectomy with 0.025%PI, as well as its safety, based on electroretinogram (ERG) and specular microscopy results.

This is the first report to describe clinical use of IVI of PI in human eyes.

Methods

Preparation for IVI of PI

In this study we used sealed PI (ISODINE SOLUTION10%: Mundipharma K.K., Tokyo, Japan) that passed sterile test (Fig. 1). First, 0.1 mL of 10%PI, which is an undiluted solution of PI, was taken into a 1-mL syringe. The needle was then changed to a new one to avoid intake of PI into the first needle, and 0.7 mL of saline solution was added, resulting in 0.8 mL of solution. This was mixed well to achieve a uniform concertation. We then reduced this to 0.1 mL (i.e., to 0.1 mL of 1.25%PI), which was used for IVI with a 30-G needle. Assuming the vitreous volume to be 5 mL, the vitreous concentration of PI was calculated to be 0.025%, the same intraocular concentration of PI as the 0.025%PI-BSS PLUS that we previously used as irrigation solution for vitrectomy in eyes with endophthalmitis.[12]

Clinical Study and Methods

This was a prospective case series study. Nine eyes of 8 patients who underwent IVI of 0.1 mL of 1.25%PI followed by vitrectomy using 0.025%PI irrigation solution for postoperative or endogenous endophthalmitis at the Nihon University Hospital between April 2015 and October 2017 were studied. This study was approved by the Ethics Committee of Nihon University Hospital (no. 20150303, approved on March 12, 2015). All procedures conformed to the Declaration of Helsinki, and informed consent was obtained from all patients who participated in this study.

All patients had been referred to our hospital under a diagnosis of either postoperative endophthalmitis or endogenous endophthalmitis. First, anterior chamber fluids were sampled for bacterial culture, after which we attempted to obtain vitreous fluids but failed in all cases due to the difficulty with aspirating the vitreous. After these attempts, IVI of 0.1 mL/1.25%PI was immediately performed. These procedures were performed on an outpatient basis at our hospital under topical anesthesia using 4% lidocaine with draping in routine sterile fashion, covering the lashes from the operative field and disinfecting the operative field with 0.25%PI (10%PI diluted with physiological saline).

Next, the patients underwent systemic medical check-ups and were hospitalized on the same day. It takes approximately 3 to 5 hours from injection of PI at the outpatient clinic until the start of vitrectomy in the operating room, because the thorough medical check-up is time consuming, informed consent for vitrectomy must be obtained, and so on.

Emergency vitrectomy was conducted on the same day as IVI of PI in 7 eyes, all but case 1, who had bilateral endogenous endophthalmitis with relatively mild inflammation. We thus assessed his general condition in detail before surgery, such that the procedures for endogenous endophthalmitis were conducted 3 days after the IVI of PI. In all cases,

25-G vitrectomy (Alcon Surgical, Fort Worth, TX) was performed under retrobulbar anesthesia. All patients were draped in routine sterile fashion, covering the lashes from the operative field. The eyelid skin was disinfected with 10%PI (i.e., undiluted) and the conjunctiva was disinfected with 0.25%PI.

In the operating room, as preparation for vitrectomy, BSS solution (Alcon Laboratories) was mixed with oxiglutathione (Alcon Laboratories). The resulting solution was a bottle of BSS PLUS to which 1.25 mL of 10%PI had been added to obtain 0.025%PI in the BSS PLUS (0.025%PI-BSS PLUS). This solution was used for anterior chamber irrigation. At the start of surgery, irrigation was suspended to obtain samples from anterior chamber fluid and vitreous fluid for culture. The anterior chamber was irrigated with 0.025%PI-BSS PLUS, and if a fibrin membrane was present it was removed. After the anterior chamber irrigation just prior to vitrectomy, we mixed a new bottle of 0.025%PI-BSS PLUS, because the effectiveness of this solution against bacteria is limited to no more than 15 minutes, as we reported previously.[12] Before starting vitrectomy (i.e., just after mixing the new bottle of PI-BSS PLUS) an infusion cannula was kept open to drain off approximately 50 mL of PI-BSS PLUS solution, because nearly 50 mL of the previous solution would be expected to remain in the vitrectomy machine. Then, using the second 0.025%PI-BSS PLUS bottle, vitrectomy was resumed. In three eyes with endogenous endophthalmitis, cataract surgery with intraocular lens (IOL) implantation was performed simultaneously to improve visualization during vitrectomy. In an eye with an IOL, if a posterior capsule was present then it was incised and widely opened to allow fluid circulation from the vitreous cavity to the anterior chamber. If no posterior vitreous detachment existed, one was carefully created while avoiding retinal tear formation. Peripheral vitrectomy was also conducted to the extent possible. At the completion of vitrectomy, anterior chamber fluid and vitreous fluid were again obtained for culture. The scleral and conjunctival wounds were closed with one Vicryl 8-0 (Ethicon, Cornelia, GA) suture to ensure tight closure of the scleral wound. After wound closure, vancomycin (Shionogi, Osaka, Japan) 1 mg/0.1 mL and ceftazidime (Pfizer, New York, NY) 2 mg/0.1 mL were injected intravitreally. After vitrectomy, imipenem hydrate/cilastatin sodium 0.5 g (MDS, Tokyo, Japan) was infused intravenously four times daily for 5 days. Starting on day 1 after surgery, 1.5% levofloxacin ophthalmic solution (Santen, Osaka, Japan) and 0.5% cefmenoxime hydrochloride ophthalmic solution (Senju, Osaka, Japan) were administered six times daily. All patients were hospitalized for 7 to 10 days after the vitrectomy.

For bacteriological study, the intraocular fluid samples were inoculated into Kenkipota II (Clinical Supply; Kakamigahara, Gifu, Japan) for enrichment and then plated onto blood agar, chocolate agar, CHROMagar (Cosmo Bio, Tokyo, Japan), and MacConkey agar (Nihon Pharmaceutical, Tokyo, Japan) for isolation of bacterial colonies.

Corneal epithelial damage, anterior chamber inflammation, and vitreous inflammation were assessed and fundus examinations were performed daily starting day 1 after surgery using a slit-lamp microscope and indirect ophthalmoscopy. Furthermore, specular microscopy (TOMEY CORPORATION, Nagoya, Japan) was conducted for all cases before IVI and 1 to 3 months after the surgery. Postoperatively, Goldmann perimetry was also conducted 1 to 3 months after the surgery in all patients except case 7.

Pre-IVI and postoperative ERG recordings were obtained in five eyes of four cases. In two eyes of two cases, only postoperative ERG was performed. ERG was conducted employing the following methods.

Electroretinography

ERG recordings were performed before IVI and 1 to 3 months after surgery. Single flash, full-field, mixed rod and cone ERG, oscillatory potentials (OPs), and flicker ERG were recorded with the LE 4000 (TOMEY CORPORATION) using a contact lens electrode with built-in white light-emitting diodes (LEDs; LW-103; Mayo, Inazawa, Japan), which served as both the stimulus source and the recording electrode. The reference electrode was a silver plate placed on the forehead and the ground electrode was attached to one ear lobe. The patient's pupils were fully dilated with topical 0.5% tropicamide and 0.5% phenylephrine hydrochloride, and the eyes were dark-adapted for 20 minutes before the scotopic recordings, and light-adapted for 10 minutes before the photopic recordings. The ERGs were elicited by flashes of white light from a white LED. The flash ERG was elicited with white flashes delivered at an intensity of 30 cd·s/m^2, so-called dark-adapted 30.0 ERG.[15] The flicker ERG was elicited with white pulses delivered at 3 cd·s/m^2 on a white background of 30 cd/m^2 (white background) with a frequency of 30 Hz, so-called light-adapted 3.0 flicker ERG.[15] The ERGs were recorded at a sampling rate of 4 kHz with

an ERG recording system (LE-4000; TOMEY CORPORATION). The responses were filtered with a hardwired band pass filter between 0.3 and 340 Hz to record the a- and b-waves, between 75 and 340 Hz to record the OPs, and between 0.3 and 340 Hz to record the flicker ERG. The analysis time was 100 ms. All ERGs were recorded according to the standards of the International Society of Clinical Electrophysiology of Vision.[15]

The amplitudes and implicit times of the a- and b-waves were analyzed. Briefly, the amplitudes of the a-waves were measured from baseline to the troughs of the a-waves, and the amplitudes of the b-waves were measured from the troughs of the a-waves to the peaks of the b-waves. The amplitudes of the OPs were obtained by summing the amplitude measurements of the three major peaks from adjacent troughs. The implicit times of the a- and b-waves were measured from stimulus onset to the peak of each wave. The implicit times of the OPs were obtained by summing the implicit time measurements of the three major peaks from the stimulus onset.

Paired *t*-tests were performed to evaluate the differences between affected and healthy fellow eyes and those before IVI versus after surgery in an affected eye. A *P* value of less than 0.05 was taken to indicate a statistically significant difference.

Results

We performed IVI of 1.25%/0.1 mL PI (final vitreous concentration: 0.025%) and vitrectomy using 0.025%PI-BSS PLUS in nine eyes of eight patients with endophthalmitis. The clinical data of all eight patients are shown in Table 1. In all but case 7, visual acuity showed good recovery. In three eyes, cultures were positive. In case 5, even after vitrectomy, *Staphylococcus warneri* was detected but visual recovery was good. *E. faecalis*, which is thought to exert strong toxicity and to be associated with a poor visual prognosis, was detected in two cases. However, in one of these patients, case 3, dramatic improvement of endophthalmitis was nonetheless observed. In case 7, endophthalmitis developed after vitrectomy for proliferative diabetic retinopathy, which initially yielded negative culture results. However, a second vitrectomy was necessitated by a severe fibrin reaction and this resulted in a poor visual outcome.

In all patients, including cases 3, 5, 7, and 8 in which specular microscopy was not possible due to corneal edema before IVI, specular microscopy became feasible after recovery from endophthalmitis, and cell density was maintained above 2300/mm^2 in all cases.

Goldmann perimetry revealed no apparent visual field defects, except in cases 7 and 8. In case 7, visual acuity showed severe deterioration and the perimetry test was thus not conducted. In case 8, partial depression was noted on perimetry, but this corresponded to a whitened retina due to endophthalmitis.

ERG recordings were performed both before IVI and after surgery in five eyes; both eyes in case 1, and the affected eye in cases 4, 5, and 6, and only after surgery in two eyes, cases 2 and 3. The ERG parameters are all shown in Table 2.

The amplitude and the implicit times before IVI and after surgery in five affected eyes, in cases 1, 4, 5, and 6, are shown in Figure 2. The OP amplitudes in the dark-adapted 30.0 ERG and the flicker ERG after surgery were significantly higher than those before IVI. The other components did not show significant changes in amplitudes after surgery. The implicit time of the a-wave was shorter after than before IVI. The implicit times in other components did not show significant changes after surgery.

The amplitudes and the implicit times in the affected and healthy fellow eyes in five patients, cases 2, 3, 4, 5, and 6, are shown in Figure 3. No significant differences in the amplitude or the implicit time were observed in any of the components between the affected eye and the healthy fellow eye.

Discussion

Bacteria increase exponentially in the log phase.[13,14] Therefore, concerning the initial treatment of endophthalmitis, IVI of vancomycin or ceftazidime is recommended,[16] though multidrug-resistant organisms resistant to both of these antibiotics have been reported.[17] Furthermore, 8 hours are required for vancomycin to exert its bactericidal action.[18] Adjusting the concentrations of antibiotics for IVI is also rather complicated. Even if a diagnosis of endophthalmitis has been confirmed in an ophthalmology clinic, it might not be feasible to prepare these drugs. On the other hand, IVI of PI, as described in this report, exerts a rapid bactericidal effect, taking only 15 seconds to kill bacteria at the PI concentration that we use.[19] PI has bactericidal effects even against multidrug-resistant bacteria[3] and the development of drug resistance is not an issue. In addition, the concentration of PI used for IVI can easily be adjusted, as we described earlier. PI is available in worldwide, even in developing countries. Therefore,

Table 1. Patient Characteristics

Case	Patient Details	Laterality	Cause of Endophthalmitis	Days of Symptom Presentation	Preoperative Visual Acuity	Postoperative Visual Acuity
1	78, M	R	Endogenous (streptococci)	20	0.2	0.3
		L		20	0.8	1
2	50, M	R	Cataract surgery	4	1	1
3	85, F	L	Cataract surgery	1	h.m	1
4	87, M	R	Cataract surgery	2	h.m	1
5	68, F	L	Cataract surgery	10	h.m	1.5
6	70, M	R	Vitrectomy for ERM	2	h.m	1.2
7	76, M	L	Vitrectomy for PDR	2	l.s	h.m
8	49, M	R	Endogenous	2	0.01	0.4

AC, anterior chamber; M, male; F, female; L, left; R, right; h.m, hand motion; l.s, light sense; N, negative; n.e., not examined; VIT, vitrectomy; PEA, phacoemulsification and aspiration of cataract; CNS, coaglase negative staphylococcus; ERM, epiretinal membrane; PDR, proliferative diabetic retinopathy.

Table 1. Extended

Case	Culture			Intraocular Lens	Follow-Up, mo	Specular Microscopy, cells/mm^2 (pre-IVI/post-VIT)	Goldmann Perimetry
	AC (pre-IVI)	AC/Vitreous (pre-VIT)	AC/Vitreous (post-VIT)				
1	N	N/N	N/N	PEA+IOL implant	8	2767/2644	Almost normal
	N	N/N	N/N	PEA+IOL implant	8	2772/2696	Almost normal
2	N	N/N	N/N	Sparing	7	2351/2586	Normal
3	*E. faecalis*	n.e.	n.e.	Sparing	3	Uncountable/2570	Almost normal
4	N	N/N	N/N	Sparing	3	2370/2453	Normal
5	N	N/CNS	N/*S. warneri*	Sparing	6	Uncountable/2358	Almost normal
6	N	N/N	N/N	Sparing	7	2621/2655	Normal
7	N	N/*E. faecalis*	N/N	Sparing	3	Uncountable/2348	n.e.
8	N	N/N	N/N	PEA+IOL implant	10	Uncountable/2665	Partial depression corresponding to retinal white lesion

IVI of PI is thought to be a more practical and thus beneficial initial treatment for endophthalmitis than IVI of antibiotics.

The safe concentration of PI for intraocular tissues and its potential toxicity have been studied in detail.[8] Naor et al.[20] reported that a PI concentration of 0.05% or less produced no endothelial cell damage in an in vitro study using cultured bovine corneal endothelial cells, while an in vivo study of a PI concentration of 0.1% or less showed no induction of changes in either the morphology or the function of the corneal endothelium. Jiang et al.,[21] using white rabbits, showed a final PI concentration of 0.16% or lower in the anterior chamber to have no adverse results on specular microscopy and pachymetry results.[21]

Trost et al.[22] conducted a study of intravitreal PI injection in rabbits and found that ERG showed no abnormalities when the intravitreal PI concentrations were no more than 0.027% (injection of 0.1 mL containing 0.4 mg PI into the rabbit vitreous with a volume of 1.5 mL). Moreover, there were no

Table 2. Electroretinographic Parameters in All Eyes

			Amplitude, μV									
			Pre-IVI					Postsurgery				
Case	Laterality	Affected	a-wave	b-wave	b/a ratio	OPs	Flicker	a-wave	b-wave	b/a ratio	OPs	Flicker
1	R	✓	223.5	285.3	1.28	67.8	41.5	369.3	344.8	0.93	49.3	59.0
	L	✓	242.8	308.0	1.27	95.3	47.5	314.8	386.0	1.23	54.8	51.3
2	R	✓	n.e.	n.e.	n.e.	n.e.	n.e.	353.8	512.8	1.45	113.5	58.5
	L		n.e.	n.e.	n.e.	n.e.	n.e.	301.3	433.5	1.44	126.8	89.0
3	R	✓	n.e.	n.e.	n.e.	n.e.	n.e.	312.0	427.0	1.37	78.0	59.5
	L		n.e.	n.e.	n.e.	n.e.	n.e.	274.3	462.0	1.68	51.3	61.3
4	R	✓	402.0	390.8	0.97	107.8	75.0	322.3	359.5	1.12	118.3	108.3
	L		362.8	356.5	0.98	109.5	118.3	344.0	395.5	1.15	130.8	115.8
5	R		460.8	616.3	1.34	115.8	126.0	331.5	483.0	1.46	109.0	117.0
	L	✓	320.8	531.5	1.66	82.5	53.8	328.8	472.8	1.44	84.8	71.8
6	R	✓	174.0	236.0	1.36	66.5	40.3	306.8	340.5	1.11	82.0	57.8
	L		402.3	387.8	0.96	132.0	136.5	323.5	374.0	1.16	162.8	111.8

Affected, affected by endophthalmitis.

Table 2. Extended

	Implicit Time, msec							
	Pre-IVI				Postsurgery			
Case	a-wave	b-wave	OPs	Flicker	a-wave	b-wave	OPs	Flicker
1	11.3	45.3	67.3	33.3	11.0	66.5	122.8	34.0
	12.3	45.0	102.1	33.0	11.3	74.3	123.8	34.8
2	n.e.	n.e.	n.e.	n.e.	11.0	59.8	119.0	28.3
	n.e.	n.e.	n.e.	n.e.	11.0	61.8	117.3	26.3
3	n.e.	n.e.	n.e.	n.e.	14.3	74.5	114.3	26.0
	n.e.	n.e.	n.e.	n.e.	14.5	74.8	119.3	28.5
4	13.5	78.3	116.5	26.0	12.5	59.3	119.5	27.3
	12.0	51.8	117.8	26.0	11.8	62.0	117.3	26.5
5	10.8	40.5	115.3	26.8	11.8	45.8	73.8	26.3
	16.5	47.8	145.5	29.0	13.8	48.0	127.0	28.3
6	15.3	80.3	151.3	28.5	14.0	55.0	115.5	29.3
	12.8	44.0	84.0	25.0	12.3	76.8	110.3	25.3

histopathologic abnormalities in the vitreous, retina, or optic nerve. Whitacre and Crockett[23] also studied IVI of PI in rabbit eyes. When the intravitreal PI concentration was 0.3% (5%/0.1 mL), four of four rabbit eyes developed iritis, cataract progression, full-thickness retinal necrosis, and ERG amplitude reductions. When the intravitreal PI concentration was 0.03% (0.5%/0.1 mL), one of 10 eyes showed transient iritis and ERG attenuation in the a- and b-wave 1 week after injection, together with histopathologic findings of retinal edema and intraretinal necrosis in part of the inferior retina, but no changes in the lens or the vitreous body.

From the above findings, the safe intravitreal PI concentration for intraocular tissues, including both the cornea and the retina, was estimated to be no more than 0.027%.

The in vitro study of Van den Broek et al.[24] demonstrated PI to exert a bactericidal effect at concentrations of 0.005% and higher. In addition, Brozou et al.[25] performed IVI of PI in rabbit eyes with *Staphylococcus epidermidis* endophthalmitis ($n = 10$) and reported that at an intravitreal PI concentration

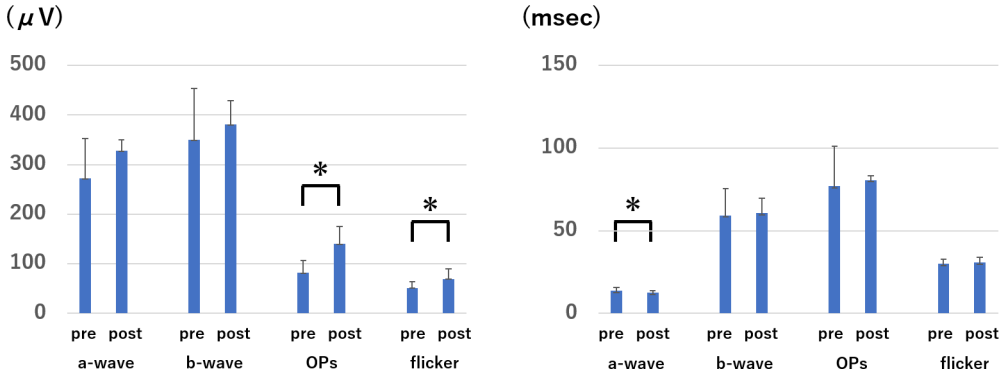

Figure 2. Comparisons of the amplitudes (*left*) and the implicit times (*right*) in each ERG component before IVI and after surgery in five affected eyes. The amplitudes of OPs and the flicker ERG after surgery were significantly higher than those before IVI. The amplitudes in other components did not show significant changes after surgery. The implicit time of the a-wave was shorter after than before IVI. The implicit times for other components did not show significant changes after surgery. pre: pre-IVI, post: post-surgery. *Bar* = standard deviation, $*P < 0.05$.

of 0.00625% (0.1%/0.1 mL) produced no clinical improvement, while 0.013% (0.2%/0.1 mL) was effective. However, flare persisted in the vitreous after injection, but the inflammation gradually subsided and vitreous culture after 1 month yielded no *S. epidermidis*.[25] From these findings, addition of PI at a concentration in the range from 0.013 to 0.027 to irrigation solution was thought to be a safe and effective treatment for endophthalmitis. Therefore, we selected an intravitreal concentration of 0.025% PI for the treatment of endophthalmitis and documented that there were no apparent clinical adverse effects or complications.[12] However, in our previous report, we were not able to evaluate clinical safety based on using ERG, Goldmann perimetry, and specular microscopy.

Recently, Kim et al.[26] reported a single injection of either 0.1%/0.1 mL or 0.3%/0.1 mL PI to be effective for treating *S. epidermidis* endophthalmitis (intravitreal concentrations of 0.0067% and 0.02%, respectively, assuming the vitreous volume of a rabbit to be 1.5 mL). Of 10 eyes studied, six and seven, respectively, demonstrated no bacterial growth on day 14. Furthermore, injections repeated three times every second day demonstrated no bacterial growth in any of the 10 eyes even at low concentrations. They also revealed that the half-life of PI was approximately 3 hours in the vitreous and, furthermore, that ERG and histologic examinations of the retina confirmed that both 0.1% and 0.3%PI were tolerable.

Thus, IVI of PI appears to be useful not only for preventing the growth of bacteria, as an initial treatment, but also for actually curing endophthalmitis without the need for administration of antibiotics. In cases with endogenous endophthalmitis especially, extra time might be needed before performing vitrectomy because a general systemic check-up should be performed. Moreover, these patients might

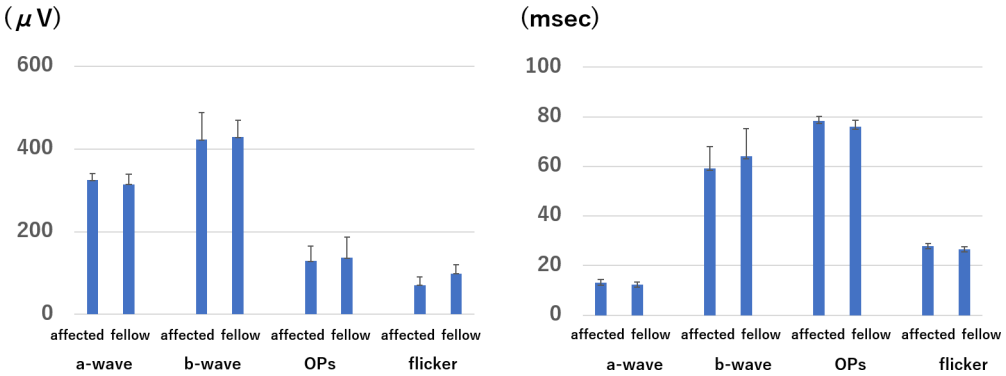

Figure 3. Comparisons of the amplitudes (*left*) and the implicit times (*right*) in each ERG component between the affected eye and the healthy fellow eye after surgery in five cases. Neither the amplitude nor the implicit time showed significant differences in any of the components between the affected eye and the healthy fellow eye. *Bar* = standard deviation.

not be candidates for surgical treatment due to poor systemic condition. In such cases, repeated IVI of PI might be an effective alternative therapy.

Endophthalmitis caused by endotoxin has been reported.[27,28] Therefore, even after disinfection to eliminate bacteria, the physical removal of bacteria is optimal for reducing inflammatory reactions. Our experience indicates that a single IVI of PI followed by vitrectomy, using a vitreous PI concentration of 0.025%, is a highly beneficial treatment for endophthalmitis.

In this study, we obtained relatively good visual outcomes except in case 7. Notably, in case 3, *S. faecalis*, which is reportedly associated with poor visual outcomes,[29] was detected in fluid from the anterior chamber before IVI of PI. Though we failed to obtain samples after treatment in this patient, visual recovery was good. We found that PI worked very effectively for the treatment of endophthalmitis. In case 5, even though *S. warneri* was detected after vitrectomy, recovery was good, suggesting that the bacteria might have represented contamination or that our PI regimen might not kill all bacteria under certain conditions.

We demonstrated the clinical safety of IVI of PI followed by vitrectomy with 0.025%PI-BSS PLUS by using ERG, Goldmann perimetry and specular microscopy, and have also taken previous experimental reports into account. Based on all measurement methods applied, no apparent adverse events were detected. Most notably, the ERG results before IVI and after surgery in the affected eye and the postoperative ERG in the affected versus unaffected eyes were compared, confirming the safety of our PI regimen for the retina. Furthermore, the perioperative ERG showed improvement in the amplitudes of the OPs and flicker ERG and in the implicit time of the a-wave, suggesting functional recovery in the retinal outer and inner layers after this therapy.

The combination of a b/a ratio less than 1.0 and early onset of endophthalmitis has been reported to be associated with a poor prognosis for postoperative endophthalmitis patients.[30] In all of our cases, the b/a ratio was higher than 0.96, which may explain why most of our cases had good visual outcomes.

The combination of PI and antibiotics may represent the additive effects of two on each other.[31] Endophthalmitis can result in vision-threatening complications, necessitating maximally aggressive therapy. In this study, we used PI-BSS PLUS, which exerts efficacy for only 15 minutes,[12] as an irrigation solution for vitrectomy. At the completion of surgery, PI-BSS PLUS is thought to have no lingering antibacterial effects, such that IVI of antibiotics might be effective for maintaining a postoperative intraocular environment free of bacterial. However, postoperative hemorrhagic occlusive retinal vasculitis associated with intracameral vancomycin as prophylaxis during cataract surgery has been reported.[32,33] We thus must be cautious when administering antibiotics directly into the eyes.

The major limitation of this study is that we failed to obtain vitreous samples before IVI of PI. Therefore, whether a single IVI of PI before vitrectomy is effective for killing bacteria remains unknown, though the samples obtained at the beginning of vitrectomy were negative except in cases 5 and 7. Furthermore, the number of cases is small and we therefore need to accumulate more endophthalmitis cases managed employing this strategy.

In this report we used an unopened PI bottle (ISODINE SOLUTION10%: Mundipharma K.K.), which had passed a sterility test. However, contamination of PI with *Pseudomonas cepacia* has previously been reported.[34] Therefore, we recommend using sterile PI, if available. In some countries, such as the United States, 5% sterile PI is available. Under such conditions, we recommend adding 2.5 mL of 5%PI to a 500-mL bottle of BSS PLUS resulting in 0.025%PI irrigation solution, which is the same concentration as that used in this study. To make 1.25%PI for IVI, 0.1 mL of 5%PI should be added to 0.3 mL of saline solution, followed by reduction to 0.1 mL. This will achieve 1.25%PI/0.1 mL for IVI.

Endophthalmitis fully resolved in all of our patients receiving IVI of PI followed by vitrectomy using 0.025%PI solution. No adverse events or complications were detected by perimetry, specular microscopy or even detailed ERG. IVI of PI is thus considered to be an optimal initial treatment for endophthalmitis. Furthermore, following IVI of PI with vitrectomy using PI is also effective for rapidly resolving endophthalmitis and achieves good visual outcomes. To our knowledge, this is the first report describing IVI of PI in human eyes.

Acknowledgments

Disclosure: **H. Nakashizuka**, None; **H. Shimada**, None; **T. Hattori**, None; **K. Tanaka**, None; **Y. Kitagawa**, None; **K. Shinoda**, None

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