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ORIGINAL RESEARCH

Quantitative Assessment of Ophthalmic Viscosurgical Devices on Visibility, Spreadability, and Durability as Corneal Wetting Agents for the Wet Shell Technique

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ABSTRACT

Purpose: To evaluate ophthalmic viscosurgical devices (OVDs) as corneal wetting agents for the wet shell technique, a common procedure in Japan to maintain the wettability of corneal surfaces.

Methods: We surveyed Japanese ophthalmologists to determine the current state of the wet shell technique. After developing three ex vivo testing methods, we evaluated the corneal wetting properties of OVDs including 3% hyaluronic acid (HA) solution and OVD products, Opegan, Opelead, Viscoat, Shellgan, Discovisc, and Opegan-Hi.

Results: Overall, 214 ophthalmologists (70%) had performed the wet shell technique, and 91% of ophthalmologists who performed vitreous surgery had performed this technique. Using a questionnaire, we evaluated the performance of OVD as corneal wetting agents as follows: (i) visibility, smoothness of OVD surface; (ii) spreadability, coverage of the cornea; and (iii) retention durability, residual ratio of OVD on the corneal surface. The smoothness and spreadability of Opegan, Opelead, and 3% HA were superior to other OVDs. Adding an appropriate amount of balanced salt solution to the other OVDs improved smoothness and spreadability similar to that of Opelead or 3% HA. Shellgan and Viscoat, combination OVDs consisting of 3% HA and 4% chondroitin sulfate, showed high retention durability, resulting in remaining longer on the cornea compared with other OVDs.

Conclusions: Physical properties of OVDs tested in this study may provide useful information for ophthalmologists to select a suitable OVD when performing the wet shell technique.

Keywords: Chondroitin sulfate; Corneal wetting agents; Hyaluronic acid; Ophthalmic viscosurgical devices; Wet shell technique

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Key Summary Points

Why carry out this study?

Ophthalmic viscosurgical devices (OVDs) are used to protect the corneal surface from damage due to drying during ocular surgery, and such treatment is called the wet shell technique in Japan. However, ophthalmologists should select an appropriate OVD for each surgery on the basis of their experience and because there are no clear criteria for usage.

We evaluated the physical properties of OVDs to reveal the criteria required to assess corneal wetting agents during ocular surgery.

What was learned from the study?

We demonstrated that each OVD product on the market has unique physical properties such as visibility, spreadability, and retention durability that make them desirable as cornea wetting agents for ophthalmologists.

We revealed that a combination of OVDs consisting of 3% hyaluronic acid and 4% chondroitin sulfate can be a versatile corneal wetting agent, applicable to various ocular surgeries. Our results provide ophthalmologists with supportive information that can be used to select a suitable OVD.

INTRODUCTION

Ophthalmic viscosurgical devices (OVDs) are divided into two types based on their cohesion-dispersion index: cohesive and dispersive [1]. Cohesive OVDs protect corneal endothelium from mechanical trauma during cataract surgery or penetrating keratoplasty by maintaining space in the eye through its high viscosity [2]. Dispersive OVDs spread easily and uniformly, adhere to tissues, and coat the corneal endothelium to protect against ultrasonic waves during cataract surgery [3, 4]. To benefit from their physical properties, a soft shell technique was developed for cataract surgery, which involves using dispersive and cohesive OVDs in sequence [1].

Routine cataract surgery takes approximately 15 min to perform, and triple surgery, including cataract extraction, intraocular lens implantation, and keratoplasty performed continuously, takes approximately 60 min [5]. When cataract and vitreous surgery are performed continuously, the procedure takes at least 120 min [6, 7]. Management of corneal conditions to prevent drying is important for maintaining visibility in the surgical field for surgeons as well as the quality of life for patients. In such circumstances, OVDs are commonly used to maintain corneal moisture during ocular surgery. The procedure using OVDs as corneal wetting agents is commonly termed the wet shell technique in Japan [8, 9]. Dispersive OVDs are usually used and their usefulness as corneal wetting agents was demonstrated in clinical studies [8–13]. However, we have no systematic data showing how the technique is performed clinically. Furthermore, we have poor information on which OVD is effective for the wet shell technique. Because there are no clear standards for the application of OVDs as corneal wetting agents, surgeons must select appropriate OVDs on the basis of their experience.

First, we investigated the physical properties of OVDs for the wet shell technique by surveying ophthalmologists using a questionnaire. Next, on the basis of the results, we evaluated the performance of OVDs as corneal wetting agents using three newly developed quantitative methods. Our results are the first evidence showing the physical properties of OVDs for effectively performing the wet shell technique based on information from a clinical survey.

The purpose of this study is to evaluate quantitatively the physical properties (visibility, spreadability, and durability) of OVDs as corneal wetting agents which are required in intraocular surgery.

Table 1 Questions and answers regarding the wet shell technique

No.	Question content	Answer options	Respondents
Q1	In cataract surgery, glaucoma surgery, or vitreous surgery do you perform the wet shell technique? (multiple choices allowed)	1. Consistently perform it 2. Sometimes perform it 3. I have not performed it	All ophthalmologists
Q2	What kind of OVDs do you select as a corneal wetting agent when performing the wet shell technique? (multiple choices allowed)	1. Cohesive type 2. Medium viscous dispersive type 3. Viscous dispersive type 4. Very low viscous dispersive type 5. Others (viscoadaptive type [1])	Ophthalmologists performing the wet shell technique who answered 1 or 2 for Q1
Q3	How important are the following four items for the expected performance of the wetting agent when performing the wet shell technique? (A) Durability on the corneal surface (B) Visibility on the corneal surface (smoothness) (C) Spreadability on the corneal surface (D) Optical enlargement on the corneal surface	1. Strong emphasis 2. Medium emphasis 3. Normal emphasis 4. Less than normal emphasis 5. Very little emphasis 6. No emphasis	
Q4	Do you adjust the surface conditions of OVD by applying balanced salt solution (BSS) when performing the wet shell technique? (answer for each surgery)	1. I consistently use BSS 2. I sometimes use BSS 3. I do not need to use BSS	
Q5	How do you apply OVD to the corneal surface as shown in Fig. 1a when performing the wet shell technique?	1. I apply OVD to the cornea center without moving the needle tip (one spot) 2. I apply OVD in a zigzag pattern to cover the corneal surface 3. I apply OVD in a spiral pattern from the center to the corneal circuit to cover the corneal surface	

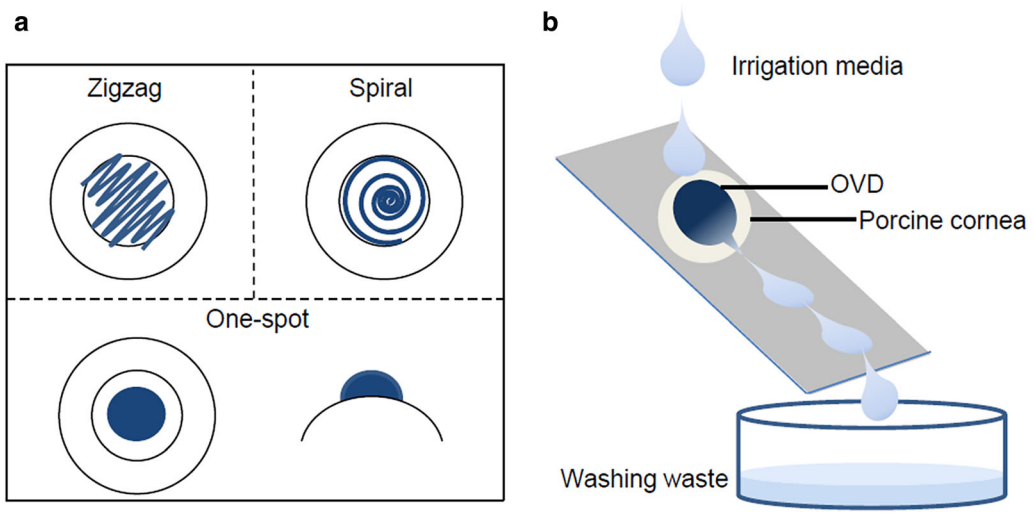

Fig. 1 Schematic illustration of methods evaluated in this study. **a** Application of OVD during the wet shell technique. **b** Method used to evaluate the residual ratio as the retention durability of OVD on the cornea

METHODS

Questionnaire Survey on Wet Shell Technique

To investigate the current status of the wet shell technique, we used a web-based questionnaire targeted at ophthalmologists who consented to answer. In the web survey conducted in December 2017 in Japan, we asked ophthalmologists five questions (Table 1). We explained that participation was voluntary and was strictly managed with personal information de-identified. The survey was conducted under the basis of the consignment agreement with Ipsos K.K. (Tokyo, Japan). Informed consent was obtained from the respondents who participated in the questionnaire survey. The questionnaire survey in this study did not require ethical reviews because the study satisfied the following criteria: (1) No handling of personal information. (2) No use of samples derived from the human body. (3) No loading on the human body. (4) It was assumed that no psychological distress would be caused.

OVDs

Table 2 shows the OVDs used in this study. Opegan®, Opegan-Hi®, and Shellgan® were purchased from Santen Pharmaceutical Co., Ltd (Osaka, Japan). Opelead® was purchased from Senju Pharmaceutical Co., Ltd (Osaka, Japan). These four products are distributed in Japan. Viscoat® and Discovisc® were purchased from Alcon Inc. (Hünenberg, Switzerland), which are distributed worldwide. A 3% hyaluronic acid (HA) solution was prepared by dissolving HA powder (derived from chicken combs, Seikagaku Corp., Tokyo, Japan) in phosphate buffered saline at a final concentration of 3%.

Porcine Eyes

We purchased porcine eyes from Tokyo Shibaurazoki Corp. (Tokyo, Japan). The eyes were harvested from 6-month-old female or castrated pigs that are a hybrid of four swine breeds, Landrace, Yorkshire, Berkshire, and Duroc. The porcine eyes were used in this study within 24 h after pigs were killed.

Table 2 OVD products investigated in this study

Bland name	Composition	Distributor	Mw (kDa)		Classification [1]	Apparent viscosity (Pa s)
			HA	CS		
Opegan	1% HA with low Mw	Santen	1100	–	Very low viscosity dispersive	5.1
Opelead	1% HA with medium Mw	Senju	1700	–	Medium viscosity dispersive	34.6
3% HA	3% HA with low Mw	Homemade	700	–	Unreported	35.2
Viscoat	3% HA and 4% CS	Alcon	700	20	Medium viscosity dispersive	61.7
Shellgan	3% HA and 4% CS	Santen	700	50	Medium viscosity dispersive	73.0
Discovisc	1.65% HA and 4% CS	Alcon	1600	20	Viscous dispersive	117.0
Opegan-Hi	1% HA with high Mw	Santen	2500	–	Viscous cohesive	62.7

Molecular weights (Mw) of HA and chondroitin sulfate (CS) and apparent viscosity of OVDs at shear rate 1 (1/s) have already been determined [14, 15]

Measurement of Smoothness of OVD Applied on Corneal Surface

Smoothness of OVD applied on the cornea was evaluated by the following procedure. Aliquots (0.05–0.10 mL) of each OVD were applied in a zigzag or spiral pattern, and photographic images of the cornea were taken using a digital camera (Keyence Corp., Osaka, Japan). Figure 2 shows typical photographs of the distortion patterns of illumination rings projected on the OVD surface. A smoothness index was established on the basis of the distortion patterns and is shown in Table 3. Three individuals estimated the distortion of the ring geometry shown in each photograph. Each sample was tested three times at room temperature (20–25 °C) according to the operating room conditions.

Measurement of Spreadability of OVD on Corneal Surface

Spreadability of OVD on the corneal surface was evaluated by comparing the coverage area of the porcine cornea, determined by analyzing photographic images using ImageJ software ver. 5.1.1.14 (Media Cybernetics, Inc., MD, USA). Briefly, 0.1 mL of OVD stained with fluorescein (Ayumi Pharmaceutical Corp., Tokyo, Japan) was applied to the porcine cornea without moving a 27-gauge needle tip at room temperature (20–25 °C). At the indicated times (0, 0.5, 1, and 2 min), corneal images were taken by a digital camera, and the covering area of each OVD was analyzed using ImageJ software. The mean area of porcine corneas used in this study was 136 ± 14 mm^2 ($n = 20$).

Measurement of Retention Durability of OVD on Corneal Surface

Porcine corneas were bound to glass slides with double-sided sticky tape, 0.1 mL of OVD was placed on the cornea center without moving the needle tip, and the glass slide was fixed at 30° (Fig. 1b). Corneas were washed with 50 mL of distilled water four times under a constant flow of 1.4 mL/s, and each wash effluent was collected to measure the amount of OVD washed out. This test was performed at room temperature (20–25 °C).

Each wash effluent was evaporated to 5 mL to evaluate the amount of OVD components, HA, or chondroitin sulfate (CS). Aliquots (100 μL) of each concentrated effluent were assayed by high-performance size-exclusion chromatography (HPSEC) using a SEC column OHpak SB-806M HQ (Showa Denko K.K., Tokyo, Japan) with 0.5 moL/L NaCl at a flow

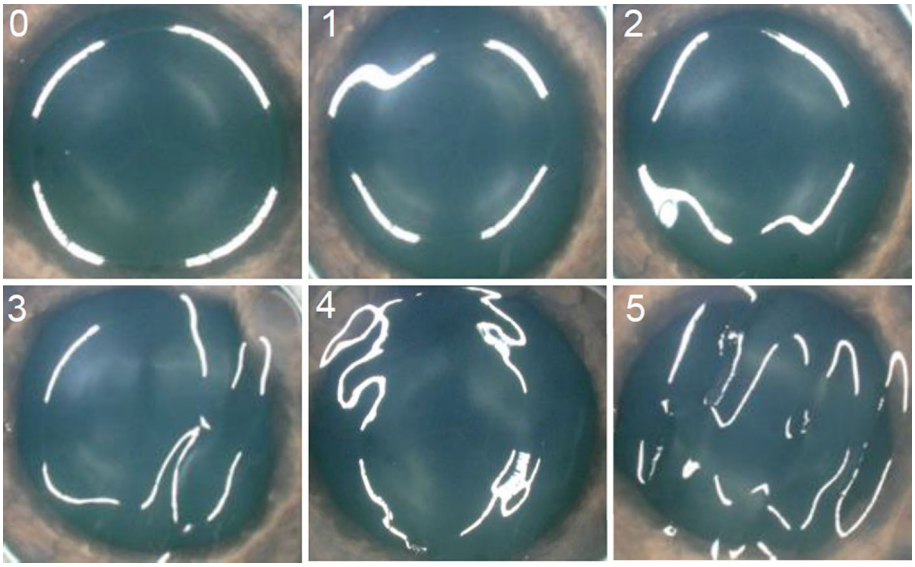

Fig. 2 Photographic images of the smoothness index of the OVD. Images of OVD surfaces placed on the cornea with the index of smoothness demonstrated by scores of 0–5

Table 3 Smoothness index of the OVD surface on the cornea

Score	Classification criteria
0	No distortion
1	Distortion is less than 1/4 of the ring
2	Distortion is less than 1/2 of the ring
3	Distortion is less than 3/4 of the ring
4	Distortion throughout the ring with
5	Many short random illumination lines assembled instead of the ring

rate of 0.3 mL/min at 35 °C. Concentrations of HA or CS contained in each sample were determined using a one-point calibration curve, in which each OVD was diluted five times as a specific standard. Amounts of OVD contained in each wash effluent were calculated as the total amount of HA and CS (if present) based on their concentrations as determined above. The residual OVD ratio on the corneal surface was calculated as follows:

$$\begin{aligned}&[\text{Residual OVD ratio after washing}(\%)]\\&= (1 - [\text{amount of OVD removed from the corneal surface (mg)}]/\\&\quad [\text{amount of OVD before washing (mg)}]) \times 100.\end{aligned} \tag{1}$$

RESULTS

Questionnaire Survey on Wet Shell Technique Targeting Ophthalmologists in Japan

Figure 3 shows the survey results. Three hundred and five ophthalmologists in Japan participated in this survey, and 70% had performed

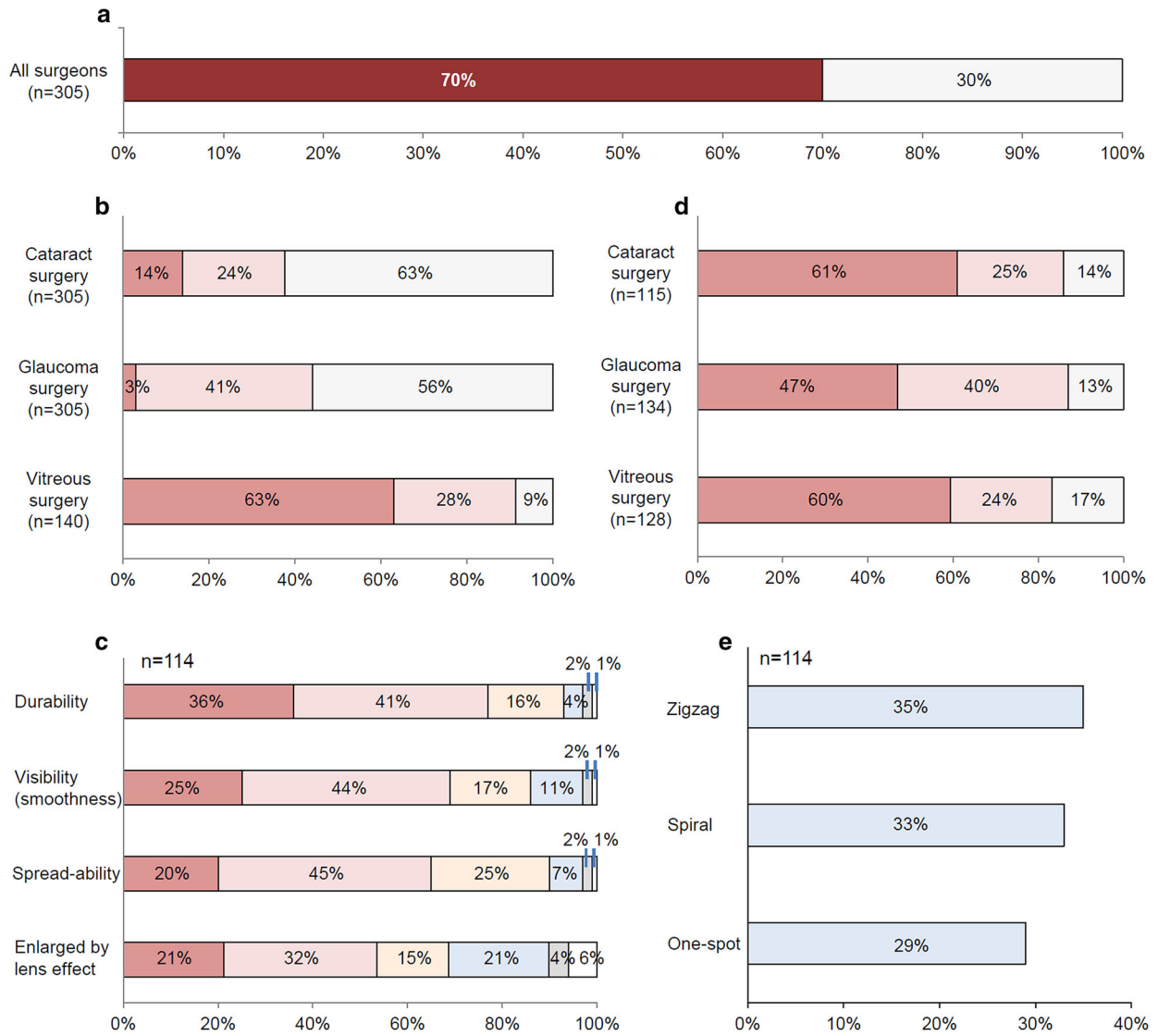

Fig. 3 Questionnaire survey on the wet shell technique. The x-axis of all graphs shows the response rate (%). **a** The rate of ophthalmologists performing the wet shell technique. Red bar, I consistently or sometimes perform the wet shell technique; white bar, I do not perform the wet shell technique. **b** Answer to Q1: The rate of ophthalmologists performing the wet shell technique in each surgery. Pink bar, I consistently perform the wet shell technique; light-pink bar, I sometimes perform the wet shell technique; white bar, I do not perform the wet shell technique. **c** Answer to Q3: The rate of valuing each physical property of OVD when performing the wet shell technique. Pink bar, strong emphasis; light-pink bar, medium emphasis; light orange bar, normal emphasis; blue bar, less than normal emphasis; gray bar, very little emphasis; white bar, no emphasis. **d** Answer to Q4: The rate of ophthalmologists applying BSS to the OVD in each surgery. Pink bar, I consistently use BSS; light-pink bar, I sometimes use BSS; white bar, I do not need to use BSS. **e** Answer to Q5: The adopting rate of the application procedures of OVD when performing the wet shell technique

the wet shell technique during ocular surgery at least occasionally. Of note, 91% of the ophthalmologists had performed the technique during vitreous surgery. We received multiple

answers for Q2 from 114 ophthalmologists, and 93% used medium viscous dispersive-type OVDs for the wet shell technique. Other OVDs were selected occasionally as follows: cohesive type, 21%; very low viscous dispersive type, 8%; viscous dispersive type, 5%; and others, 2%.

The survey results also suggested that the properties of OVDs required for use as a corneal wetting agent included (i) not disturbing visibility in the surgical field for ophthalmologists; (ii) having spreadability on the corneal surface; and (iii) maintaining retention durability.

Development of Testing Methods Using Harvested Porcine Eyes

The following testing methods were developed to evaluate the physical properties of OVD used as corneal wetting agents using harvested porcine eyes and a 3% HA solution. Spreadability was evaluated as the corneal coverage of the OVD, determined by dividing the OVD-covered area by the corneal area. Figure 4 shows the time course of the spreadability of 3% HA on the cornea. The coverage area was approximately 100 mm^2 after 2 min (Table 4).

To evaluate the property of not disturbing visibility in the surgical field, we focused on the smoothness of the OVD surface. As described above, various shaped illumination rings were observed on the OVD surface depending on the surface conditions (Fig. 2). We developed a smoothness index with reference to corneal smoothness scoring (Table 3) [16, 17]. The 3% HA score decrease was time dependent, reaching less than 2 within 10 s, which did not affect visibility (Fig. 5a, c). Therefore, we set a score of 2 at 10 s after administration as an evaluation criterion in subsequent tests.

Regarding the evaluation of the retention durability of OVD on the cornea, we developed a flow system with reference to a method for measuring the retention of dosage forms to biological surfaces [18, 19]. The residual ratio of 3% HA decreased with the number of washes, and the mean residual ratio after the fourth wash was 45% (Fig. 6).

Evaluation of Spreadability of OVD on Corneal Surface

Because the mean corneal area is 100 mm^2 in humans [20], the spreadability threshold of OVDs was set at 100 mm^2, and the corneal area was covered within 2 min after application. The coverage area of each OVD (0.1 mL) on the cornea increased with time (Table 4). Opegan exhibited the highest spreadability among OVDs tested. Its area of corneal spread reached 180 mm^2 within 1 min. Then, Opegan continued to spread throughout the eye, which suggests that the amount of OVD applied might be significantly reduced. The initial corneal coverage of Opelead and 3% HA was approximately 50 mm^2 and the area reached 100 mm^2 after 2 min. Other OVDs exhibited low spreadability. Their corneal covered area after 2 min was lower than the initial area of Opegan (99 mm^2). Instilling 0.2 mL of balanced salt solution (BSS) markedly enhanced the covered area of each OVD, and covered a corneal area greater than 100 mm^2 at 2 min after application (Table 4). Therefore, we instilled BSS at twice the amount of OVD applied, if necessary.

Effect of Administration Procedure of OVD on Corneal Coverage

The human corneal area is approximately 100 mm^2 [20]. Most OVDs were insufficient as corneal wetting agents for human surgery (Table 4). Therefore, increasing the dosage of OVD or changing the application procedure might achieve a coverage area of at least 100 mm^2. We evaluated whether application using a zigzag or spiral pattern affected the OVD corneal coverage (Fig. 1a). Distinct from the one-spot pattern, the coverage area of OVD by zigzag or spiral achieved 100 mm^2 (data not shown). We also evaluated whether the applied amounts of OVD could be reduced in these procedures. The amount of OVD could be reduced by approximately 50–70% compared with the one-spot pattern (Table 5). We evaluated the smoothness of the OVD surface on the cornea by applying the mean minimum amount of OVD.

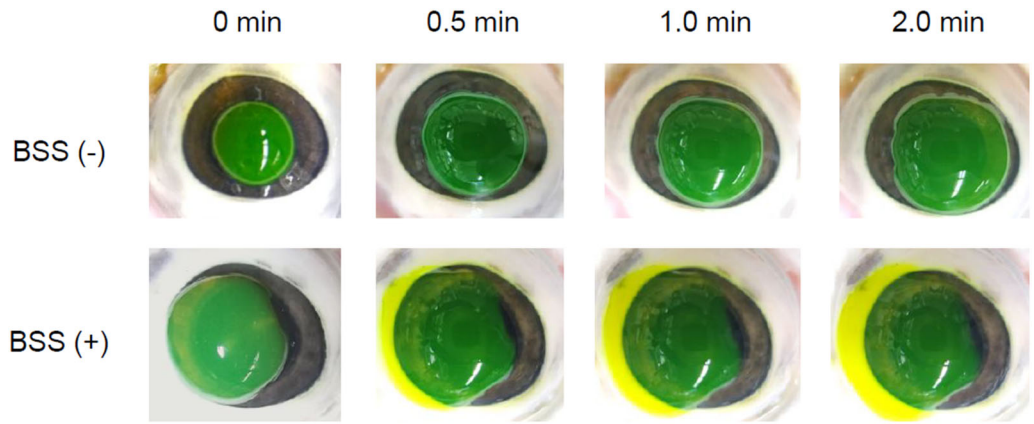

Fig. 4 Time course of the spreadability of OVDs on the cornea. Photographic images of 3% HA on the corneal surface without BSS (upper) or with 0.2 mL BSS (lower)

Table 4 Time course of the coverage area of OVDs on the cornea

OVD	Instilling of BSS	Coverage area of OVDs (mm^2)			
		0 min	0.5 min	1.0 min	2.0 min
Opegan	−	99 ± 3	162 ± 5	180 ± 6	–
Opelead	−	48 ± 8	90 ± 11	99 ± 12	111 ± 14
	+	102 ± 18	145 ± 20	158 ± 24	168 ± 28
3% HA	−	53 ± 3	82 ± 7	92 ± 8	104 ± 8
	+	92 ± 9	130 ± 10	143 ± 7	157 ± 7
Viscoat	−	43 ± 3	64 ± 5	70 ± 6	83 ± 10
	+	77 ± 16	103 ± 15	113 ± 12	122 ± 12
Shellgan	−	43 ± 4	65 ± 9	72 ± 11	82 ± 15
	+	69 ± 16	98 ± 14	106 ± 10	115 ± 11
Discovisc	−	31 ± 5	55 ± 5	60 ± 5	66 ± 4
	+	62 ± 8	91 ± 10	100 ± 12	110 ± 9
Opegan-Hi	−	38 ± 2	60 ± 8	64 ± 9	71 ± 12
	+	71 ± 7	91 ± 9	99 ± 6	110 ± 6

Without BSS (−) or with 0.2 mL BSS (+). Values represent the mean ± standard deviation (n = 3)

Evaluation of Smoothness of OVD Surface on Cornea

On the basis of the smoothness index (Table 3), we evaluated the effect of OVD on visibility in the surgical field. OVD surface distortion was reduced slightly by the spiral pattern compared with the zigzag pattern (Fig. 5a, c). The initial smoothness index of each OVD for the spiral pattern was greater than 3, except for Opegan. The index of Opelead and 3% HA was reduced to at most 2 at 10 s after administration. The rate of reduction of the index for the other four

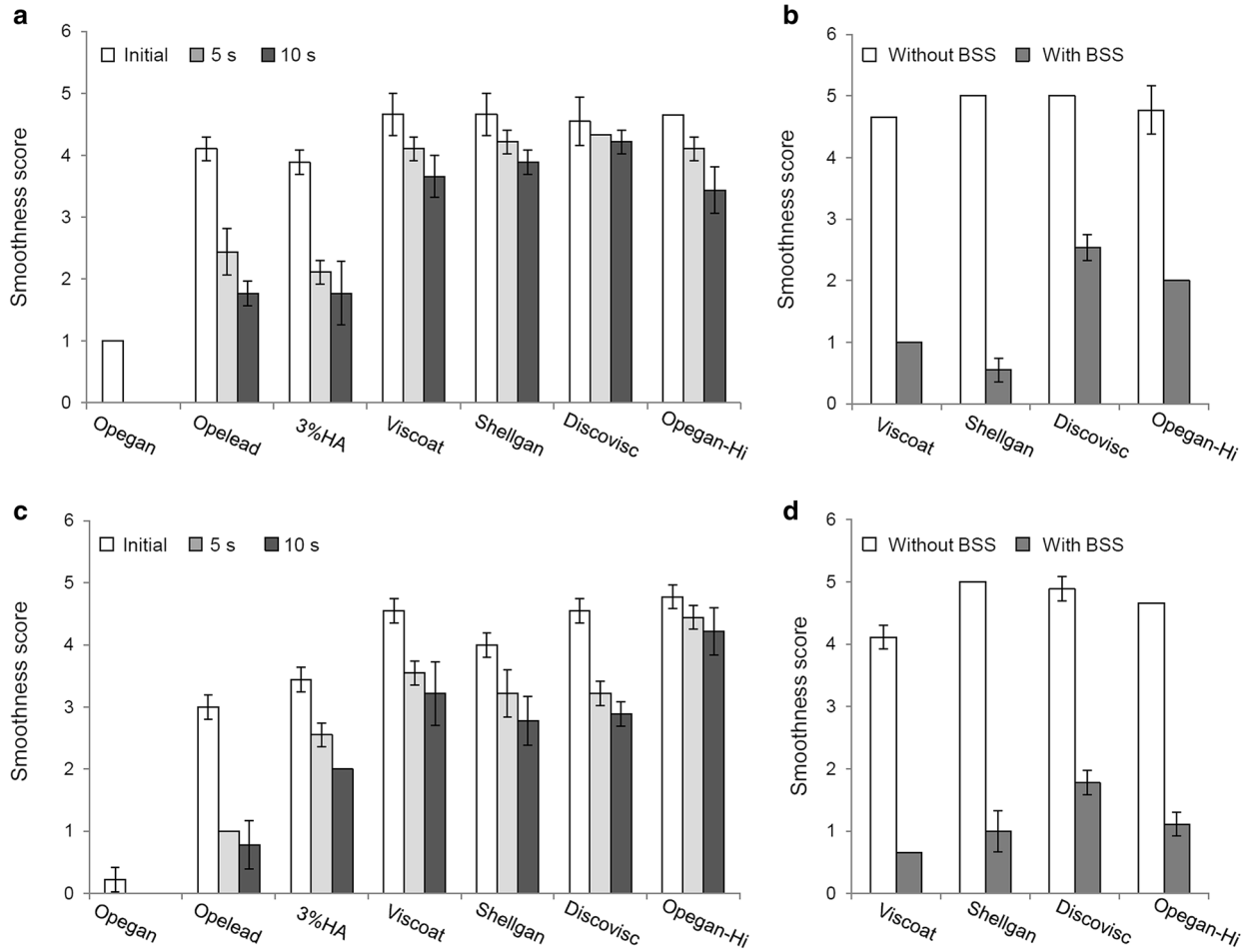

Fig. 5 Smoothness of the OVD surface with different application patterns. Time-dependent change of smoothness scores of the OVD surface by zigzag (**a**) or spiral (**c**) pattern. Change of smoothness scores of OVD surface by instilling 0.1 mL of BSS to the OVD in a zigzag (**b**) or spiral (**d**) pattern. Values represent the mean ± standard deviation (n = 3)

OVDs was very slow compared with Opelead, taking more than 1 min for their indices to go below 2 (data not shown).

Retention Durability of OVD on Corneal Surface

Regarding retention durability, we evaluated the residual ratio of each OVD on the corneal surface by the washing-out method (Fig. 6). Opegan-Hi was easily removed from the corneal surface by one wash, with a residual ratio of 25%. The second wash completely washed out the OVD applied to the cornea. The residual ratios after each wash were similar for Opegan and Opelead, which are a 1% HA product. Although Discovisc contains 1.65% HA, the residual profile was similar to that of Opegan and Opelead (mean residual ratio of them was approximately 30% after the fourth wash). OVDs including 3% HA showed high retention durability. After the fourth wash, the mean residual ratio of each OVD was as follows: Shellgan, 61%; Viscoat, 50%; and 3% HA, 45%.

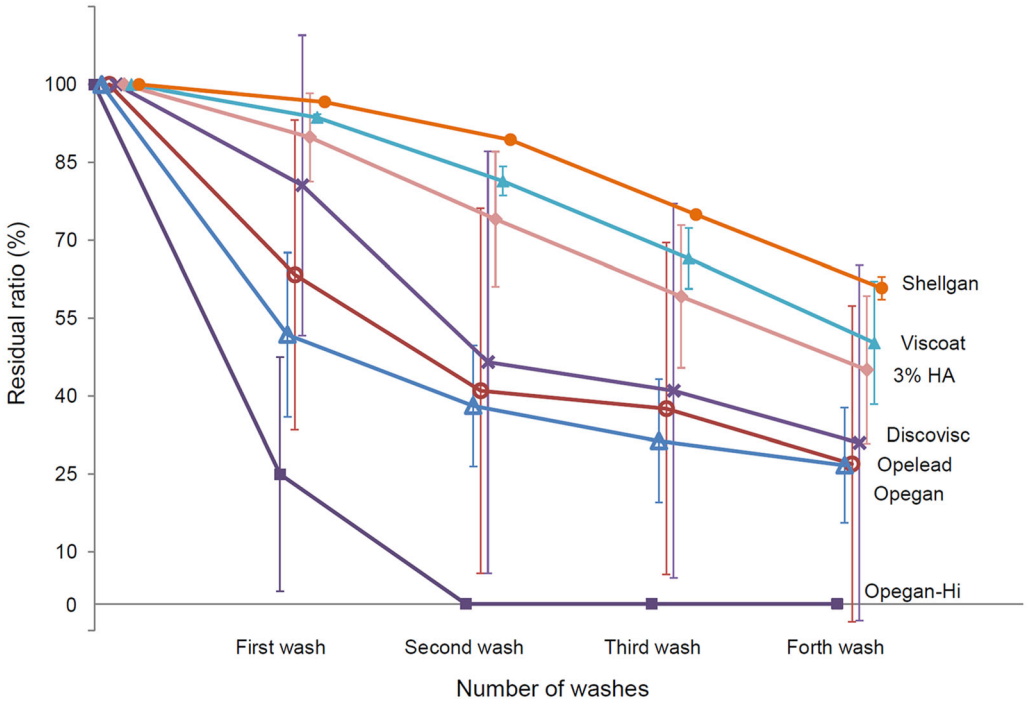

Fig. 6 Retention durability of OVDs on the cornea. Filled circle, Shellgan; filled triangle, Viscoat; filled diamond, 3% HA; cross mark, Discovisc; unfilled circle, Opelead; unfilled triangle, Opegan; filled square, Opegan-Hi. Values represent the mean ± standard deviation (n = 3)

Table 5 Minimum amount of OVD to cover 100 mm^2 of the cornea

OVD	Minimum amount of OVD (mL)	
	Zigzag	Spiral
Opegan	0.048 ± 0.007	0.050 ± 0.003
Opelead	0.064 ± 0.005	0.058 ± 0.008
3% HA	0.049 ± 0.002	0.051 ± 0.004
Viscoat	0.066 ± 0.011	0.059 ± 0.025
Shellgan	0.057 ± 0.003	0.060 ± 0.010
Discovisc	0.071 ± 0.014	0.065 ± 0.002
Opegan-Hi	0.072 ± 0.005	0.075 ± 0.013

Values represent the mean ± standard deviation (n = 3)

DISCUSSION

Prevention of corneal drying during ocular surgery is important to maintain visibility in the surgical field for ophthalmologists as well as reducing the risk for corneal epithelial damage after ocular surgery [13]. A corneal wetting procedure was developed using OVD products with reference to a soft shell technique to reduce corneal endothelial cell damage during cataract surgery. In Japan, the procedure is termed the wet shell technique [8, 9]. However, the current status of the wet shell technique is unknown. We surveyed ophthalmologists regarding the status of several issues of the technique (Table 1).

Overall, 70% of respondents (214 ophthalmologists) had used the wet shell technique in their surgeries daily, indicating the procedure is widely used by Japanese ophthalmologists (Fig. 3). Medium viscous dispersive-type OVDs were the most common corneal wetting agents in this survey (Table 1, Q2). In this study, Opelead, Viscoat, and Shellgan were classified into such a category (Table 2). We previously evaluated the physical properties of these OVD products and demonstrated that their basic properties were different even though they belonged to the same category [14, 15]. We have

speculated that the molecular weight (Mw) and concentration of HA, which is the main component of OVDs, have a great influence on rheological properties. Therefore, we hypothesized that each OVD would exhibit specific corneal wetting agent properties that depend on the Mw and concentration of its HA.

The survey results suggested that many ophthalmologists required the following properties for OVD as a corneal wetting agent: (i) not disturbing visibility in the surgical field for surgeons; (ii) spreadability on the corneal surface; and (iii) retention durability. Because this survey allowed multiple answers, the ranking of these factors was unclear. In order to complete intraocular surgery, it is necessary to avoid obstruction of the surgeon's visual field. Therefore, ensuring good visibility is an essential prerequisite for the wet shell technique. On the basis of this precondition, we considered corneal surface spreadability to be an important OVD property for maintaining corneal wettability and thereby protecting the cornea. Regarding retention durability, we considered it important to manage ocular surgery efficiently because it was related to the readministration interval of OVD. Increasing the administration frequency leads to an increase in the length of interruption during the surgical procedure.

When applied in a one-spot pattern, Opegan, a very low viscosity dispersive OVD product containing 1% HA with low Mw, covers the entire cornea immediately while maintaining a smooth surface (Table 4 and Fig. 5). This indicates that it is highly spreadable. The prompt spread may also promote good visibility on the cornea surface. Prinz et al. demonstrated that 2% hydroxypropyl methylcellulose (HPMC), a very low viscosity dispersive OVD, distributed quickly and could provide sufficient corneal wettability, suggesting its usefulness for corneal wetting during brief surgical procedures such as cataract surgery [21]. Therefore, we considered that very low viscosity dispersive OVDs, such as 1% HA with low Mw, might be suitable for use in short-term surgery. Opelead, a medium-viscosity dispersive OVD, covered a corneal area greater than 100 mm^2 in 2 min, meaning that the OVD can cover a human cornea without any additional treatment. Both Opegan and Opelead are 1% HA products that contain HAs of different Mw. Therefore, the viscosities of these products also differ (Table 2) and may account for the difference in spreadability between the two products.

A 3% solution of HA showed almost the same behavior as Opelead (Table 4 and Fig. 5). These results suggested that the properties of the corneal wetting agent in OVD products (low Mw HA) could be changed by changing the HA concentration. The area of the cornea covered by the other OVD products, Viscoat, Shellgan, Discovisc, and Opegan-Hi, was less than 80 mm^2 at 2 min after application. Because the mean area of the human cornea is 100 mm^2, the area covered by these products was insufficient for human ocular surgery.

Three options are available to improve the corneal coverage area: increasing dosage, changing the application procedure, and additional processing. Considering the volume required in ocular surgery, it is likely to decrease the dosage for the wet shell technique. The survey results showed that 68% of ophthalmologists applied OVD in a zigzag or spiral pattern instead of a one-point pattern and that BSS instillation was performed in at least 80% of ocular surgery involving the wet shell technique (Fig. 3d, e). Instillation of 0.2 mL of BSS onto each OVD resulted in achieving coverage of 100 mm^2 in all cases after 2 min (Table 4), suggesting that BSS instillation is an indispensable step in the wet shell technique. Since cataract surgery is usually completed within 20 min, it is important to minimize the time of subtreatment for corneal protection during surgery. As described above previous reports suggested that spreadability of OVDs on the cornea was related to rheological properties including viscosity [10, 21]. Considering the relationship mentioned above between HA concentration, viscosity, and spreadability, it is speculated that BSS instillation onto each OVD reduces OVD viscosity locally and as a result improves OVD spreadability.

We evaluated different application procedures as another approach (Table 5, Fig. 5). Zigzag and spiral patterns covered the entire cornea immediately after administration and reduced the dosage required. Except for Opegan

and Opelead, however, neither procedure gave satisfactory results for the smoothness of the OVD surface, which took more than 1 min to achieve a smooth surface that did not affect the surgeon's visual field. This maybe explains the low usage of OVD for the wet shell technique in cataract surgery (Fig. 3b).

Because BSS instillation smoothened out small irregularities on the OVD surface [10], we evaluated whether BSS instillation affected the smoothness of the OVD surface applied onto the cornea. Instilling 0.1 mL of BSS to Shellgan, Viscoat, Discovisc, and Opegan-Hi, which had a low surface smoothness without BSS treatment, markedly restored their smoothness (Fig. 5c, d). The smoothness score of four OVDs applied in a spiral pattern was greater than 4 initially, and decreased to less than 2 immediately after instilling BSS. Even in a zigzag pattern, the visibility was immediately improved by instilling BSS (Fig. 5b). There was no significant difference in the score between these application procedures coupled with instillation of BSS. These results demonstrate the indispensability of instilling BSS in the wet shell technique using OVDs with certain viscosities.

The retention durability of OVD was another important physical property for the wet shell technique (Fig. 3c). Several studies reported the retention durability of OVD on the cornea, evaluated by duration time or frequency of application [10, 11, 13, 21]. We considered that for low retentivity OVDs, their application frequency would consequently increase. Kwon et al. demonstrated that OVDs were more effective corneal wetting agents because their frequency of intraoperative application is low relative to BSS [13]. When performing vitreous surgery, ophthalmologists may emphasize this property because surgery takes a long time compared with other ocular surgeries. The retention durability of the OVD products including 3% HA and 4% CS, Viscoat and Shellgan, was superior to that of other OVDs, indicating that they might reduce the frequency of interruptions by intraoperative application. Although each OVD had a different residual ratio, there was no definite relationship between the retention durability and apparent viscosity. Since these OVDs have different rheological properties [14], intensive studies will be needed to determine how those differences affect retention durability.

We previously reported that the OVDs tested in this study had specific rheological properties even when they were of the same composition or classification type [14, 15]. Here, we clarified the advantages and disadvantages of each OVD for the wet shell technique on the basis of their properties. The ideal OVD spreads immediately and has long-term retention durability without affecting visibility. However, no OVD meets all requirements. Our results suggest that near-ideal properties can be achieved by combining an OVD containing 3% HA and 4% CS with BSS.

The current study has several limitations. We did not assess quantitatively the optical clarity of OVDs because of long-term retention on the cornea. In our experiments, we evaluated visibility by smoothness of the OVD surface immediately after OVD application. As evaluated in some papers, it is conceivable that visibility related to optical clarity changed as a result of prolonged retention on the cornea [11, 12, 21]. Differences in the rheological properties of OVDs might influence their performance during the wet shell technique. Further studies are needed to elucidate the detailed relationship between the properties and the performance of OVDs during ocular surgeries.

CONCLUSION

We established three methods to evaluate the physical properties of OVDs, which ophthalmologists emphasized when used as corneal wetting agents. We also compared the performance of OVD products in relation to their (i) visibility, (ii) spreadability, and (iii) retention durability. Our results provide a useful basis for the selection of OVDs for ophthalmologists performing the wet shell technique. In particular, our results suggest that combination products including 3% HA and 4% CS may be a versatile corneal wetting agent applicable to various ocular surgeries.

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Compliance with Ethics Guidelines. Informed consent was obtained from the respondents who participated in the questionnaire survey. The questionnaire survey in this study has been judged to not require ethical reviews because the study satisfied the following criteria: (1) No handling of personal information. (2) No use of samples derived from the human body. (3) No loading on the human body. (4) It is assumed that no psychological distress would be caused.

Data Availability. The datasets obtained and analysed during the current study are available from the corresponding author on reasonable request.

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