*Original Article*

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# Generic selection criteria for safety and patient benefit [IX]: Evaluation of "feeling of use" of sodium hyaluronate eye drops using the Haptic Skill Logger (HapLog®) wearable sensor for evaluating haptic behaviors

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**SUMMARY** We compared the pharmaceutical properties, such as surface tension, drop volume, nozzle inner diameter, and force to push the drug product out of the container (squeeze force), of purified sodium hyaluronate eye drops preparations of one brand-name (Hyalein) and 11 generic drugs used for treatment of keratoconjunctiva epithelial disorders, and examined product selection based on the needs of the patient. The surface tension of Nissin (51.0 dyn/cm) and Nitten (52.3 dyn/cm) was significantly lower than that of Hyalein (62.8 dyn/cm), whereas Nitten PF (69.5 dyn/cm) was significantly higher than Hyalein. The drop volume of Tearbalance (42.4 mg), Nissin (43.7 mg), and Nitten (42.7 mg) was significantly lower than that of Hyalein (50.4 mg). We compared the squeeze force using a wearable touch sensor (Haptic Skill Logger: HapLog®) and digital force gauge (DF). The squeeze force of HapLog® showed values of about 1.7- to 3.5-fold higher than that of DF. Moreover, the squeeze force of Eyecare (34.0 N), Kyorin (35.4 N), and Nitten PF (44.3 N) by HapLog® was significantly higher than that of Hyalein (10.5 N). In contrast, the squeeze force of Kyorin (20.8 N) and Nitten PF (25.0 N) by DF was significantly higher than that of Hyalein (12.2 N). Two questionnaire surveys on the feeling of instillation of eye drops revealed a strong negative correlation between feeling of use and squeeze force.

***Keywords*** HapLog®, Digital force gauge, Ophthalmic liquids/solutions, Sodium hyaluronate ophthalmic solution

## 1. Introduction

In recent years, Japan has been actively promoting the use of generic drugs (GE) from the viewpoint of optimizing or reducing medical expenses (*1*). Based on a document by the Ministry of Health, Labor and Welfare, "Changes to generic drugs listed in prescriptions" (March 5, 2012 Health Department Director General, Health Department 0305 No. 12), when a brand name is written on the drug listed in the prescription (*i.e.* brand name prescription drug), the changing and dispensing to a generic drug with a different content or similar alternative dosage form without prior confirmation by the prescribing physician is allowed (*2*). To reduce medical costs (*3,4*), the choice and selection of generic drugs are important to the pharmacist who is responsible for dispensing to the patient.

There are various types of eye drop containers, and the ease of eye drop use (*i.e.* ease of extrusion or instillation) differs depending on the container used as well as the properties of the contents (for example, viscosity) (*5*). If the container is too hard, it may be difficult for elderly people or people with weak finger strength to use; in contrast, if it is too soft, an excessive amount may be instilled at once. Such problems may to lead to poor compliance.

To date, one study has investigated the squeeze force required to instill a drop of ophthalmic solution using a digital force gauge (DF) (*5*). However, in the method of measuring squeeze force, all are different from the use of dropping an eye drop container with a finger, the container was fixed from both sides with a hemispherical urethane spherical compression jig, and the force (squeeze force) against which one was pressed with a digital force gauge was measured (*6*).

Therefore, using the Haptic Skill Logger (HapLog®), a wearable contact force sensor that allows the measurement of squeeze force by pushing the eye drop container directly with fingers (*7*), we report the evaluation of various measurements, surface tension, nozzle inner diameter and drop volume from the container, and squeeze force, and "feeling of use".

## 2. Materials and Methods

### 2.1. Materials

Ethical pharmaceutical eye drops containing purified sodium hyaluronate ophthalmic solution (one brand-name "Hyalein® Ophthalmic Solution 0.1%" and 11 generic products) were used in this study. The product name, abbreviated name, class, company name, and lot number of these products are listed in Table 1. In addition, all products are currently available on the market and registered with the Pharmaceutical and Medical Devices Agency (PMDA) (*8*). All the reagents used were of analytical grade.

### 2.2. Measurement of surface tension

The surface tension of each preparation was measured according to a previous study (*6*). Briefly, the ophthalmic solutions taken from each formulation were measured at 25 ± 1°C using a tension meter method with a Du Noüy type surface tension meter (Rigo Co., Ltd., Tokyo, Japan). Each drug was measured 6 times and the average value was calculated.

### 2.3. Measurement of drop weight

The drop weight of each preparation was measured according to a previous study (*6*). Briefly, the weight obtained by instilling one drop from each preparation was measured 6 times using an analytical balance XSE204 (Mettler Toledo Co. Ltd., Tokyo, Japan) at 25 ± 1°C, and the average value was calculated.

### 2.4. Measurement of nozzle inner diameter

The inner diameter of the ophthalmic container was measured 6 times using a digital caliper type 19974 (Shinwa Rules Co., Ltd., Niigata, Japan) and the average value was calculated.

### 2.5. Measurement of squeeze force required to instill a drop of ophthalmic solution using DF

The measurement of the weight obtained by instilling one drop from each formulation and the measurement of the squeeze force required to instill one drop of eye drop were performed according to a previous study (*6*). Each preparation was set in a holder to which a DF (ZP-50N; Imada Co., Aichi, Japan) was attached, and the handle was slowly turned to form a hemispherical urethane spherical compression jig (Imada Co., Aichi, Japan). The eye drop container was sandwiched from both sides, and the force applied at the moment when a drop was instilled was doubled to obtain a squeeze force. The doubling of the force was applied at the moment of drop instillation because the force on one side of the container, which is sandwiched from both sides, is displayed in DF measurement; therefore, we assumed that the same force was also applied from the other side. Each formulation was measured 6 times and the average value was calculated.

### 2.6. Measurement of squeeze force using HapLog®

The squeeze force of each drug product was measured using HapLog® according to a previous study (*9*). After full explanation of the purpose of this survey to the subjects (8 individuals), the RAND function of Excel was used to randomize the 12 types of eye drop containers. Then, a wearable touch sensor HapLog® (Tec Gihan Co., Ltd., Kyoto, Japan), as a tactile sensibility evaluation tool, was used to measure the pressure change applied to the fingertips for each drop, which were in a randomized order. For the measurement method using HapLog®, touch sensors were attached to the dominant thumb and index finger, and the center of the eye drop container was grasped using the thumb and index finger; the total force (thumb + index finger)

**Table 1. Eye drop products used in this study**

| Product name | Abbreviated name | Company name | Lot numbers |
|---|---|---|---|
| Hyalein® Ophthalmic Solution 0.1% | Hyalein | Santen Pharmaceutical Co., Ltd. | 1HT6404 |
| Eyecare® Ophthalmic Solution 0.1% | Eyecare | Kaken Pharmaceutical Co., Ltd. | E55320 |
| Tearbalance® Ophthalmic Solution 0.1% | Tearbalance | Senju Pharmaceutical Co., Ltd. | H564 |
| Hyalonsan® Ophthalmic Solution 0.1% | Hyalonsan | Toa Pharmaceutical Co., Ltd. | A47AK |
| Hyaluronate Na Ophthalmic Solution 0.1% "Kyorin" | Kyorin | Kyorin Rimedio Co., Ltd. | 94AA |
| Sodium Hyaluronate Ophthalmic Solution 0.1% "Nissin" | Nissin | Nissin Pharmaceutical. Co., Ltd. | 311131 |
| Hyaluronate Na Ophthalmic Solution 0.1% "Pfizer" | Pfizer | Pfizer Japan Inc. | MA02 |
| Hyaluronate Na Ophthalmic Solution 0.1% "Wakamoto" | Wakamoto | Wakamoto Co., Ltd. | 5470 |
| Sodium Hyaluronate Ophthalmic Solution 0.1% "TS" | TS | Teika Pharmaceutical Co., Ltd. | KE05 |
| Sodium Hyaluronate Ophthalmic Solution 0.1% "Towa" | Towa | Towa Pharmaceutical Co., Ltd. | A001A |
| Sodium Hyaluronate Ophthalmic Solution 0.1% "Nitten" | Nitten | Nitten Pharmaceutical Co., Ltd. | L1738C |
| Sodium Hyaluronate PF Ophthalmic Solution 0.1% "Nitten" | Nitten PF | Nitten Pharmaceutical Co., Ltd. | GF96 |

required to instill a drop was recorded as the squeeze force (N). The measurements began with the eye drops placed on a laboratory bench. The dominant hand with a tactile sensor was used to hold the eye drop container, and the other hand carried a transparent petri dish. After instilling a drop of the drug solution onto the petri dish, the eye dropper was returned to the experimental table. This operation was measured 10 times for each eye drop container. From the HapLog® measurement data, the average maximum squeeze force applied to the fingertip (average maximum pressure), the average time required from the start of pressurization to the drip (average drip time), and the average value of the total squeeze force were analyzed. This was calculated for each person and the total average was also calculated. However, among 10 repeated measurements, the first 3 were deemed as practice, and only 6 measurement replicates (measurements 4 to 9) were utilized for calculation of average. Although these can generate free touch feeling of the fingertips and allow simultaneous evaluation of wearer's finger contact force and touch feeling, calibration was performed for each wearer because individual differences due to the wearing methods and finger sizes cause an error in contact force measurement (*7*).

### 2.7. Statistical analysis

For each measured parameter, the values were compared using Dunnett's multiple comparison test or Pearson's correlation coefficient test (*10*). A $p$-value under 0.05 or 0.01 was regarded as significant.

### 2.8. Questionnaire survey using a 6-point scale

Immediately after the measurements for each eye drop, a questionnaire survey was conducted regarding the individual's feeling about the container (*i.e.* the ease of eye drop use), which was evaluated on a 6-point scale (Table 2).

**Table 2. Questionnaire survey on the feeling of applying various eye drops**

| Point score | Products symbol (A - L) |
|---|---|
| Very difficult | 1 |
| Difficult | 2 |
| Slightly difficult | 3 |
| Slightly easy | 4 |
| Easy | 5 |
| Very easy | 6 |

Questionnaire survey. We would like to ask you about your feeling when using one drop of a range of eye drops (A to L). When discharging or instilling one drop products (A to L), please circle the number showing the feeling of use. Difficult to apply represents that it is difficult to discharge or instill a single drop (it requires a pressing force, it takes time to take out). Easy to apply represents it is easy to instill a single drop, and the drop comes out smoothly. If the eye drop is easy to apply, but it is difficult to instill only one drop and you get two drops, then please circle the number with a double circle.

### 2.9. Questionnaire survey using a continuous scale of absolute values

A questionnaire survey using a continuous scale of absolute values for ease of eye drop use or instillation was conducted (Figure 1). In the evaluation, the ease of eye drop instillation was expressed in the range of 0 to 72 mm and the difficulty of instillation in the range of 0 to -72 mm. The responses to the questionnaire were evaluated by quantifying the measurement of the position marked with a circle on the scale with the distance (mm) from point 0.

## 3. Results

### 3.1. Measurement of surface tension

The surface tension of each formulation used in this experiment was measured. The results are shown in Figure 2. The surface tension of Hyalein was 62.8 dyn/cm, whereas that of ranged from 51.0 to 69.5 dyn/cm (Figure 2). In particular, Nissin (51.0 dyn/cm) and Nitten (52.3 dyn/cm) had significantly lower surface tension. In contrast, Hyalonsan (67.1 dyn/cm) and Nitten PF (69.5 dyn/cm) had significantly higher values.

### 3.2. Measurement of drop weight

The drop weight from each eye drop container used in this experiment was measured (Figure 3). The drop weight of Hyalein was 50.4 mg, whereas that of the generic drugs ranged from 42.4 to 52.2 mg (Figure 3). In particular, Tearbalance (42.2 mg), Nissin (43.7 mg),

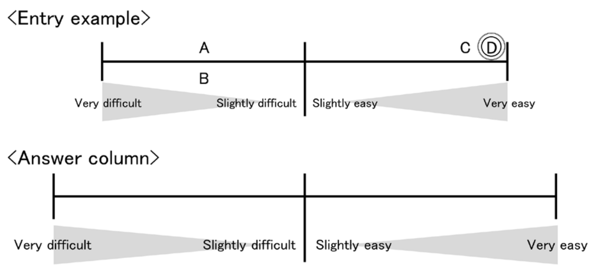


**Figure 1. Questionnaire survey on the feeling of using various eye drops (Continuous scale).** We would like to ask you about your feeling when using one drop of a range of eye drops (A to L). In the scale below, the left side of the center is somewhat hard to instill/discharge a drop, the right side is somewhat easy to instill; the closer to the left end, the more difficult to instill; the closer to the right end, the more easily to instill. When instilling one drop of each of the eye drops (A to L), enter the product code in the position of the feeling of use that fits the scale below. Difficult to apply indicates that it is difficult to instill one drop (requires a pressing force, takes time to instill, *etc.*). Easy to apply indicates that it is easy to instill one drop, and one drop comes out smoothly. If it is easy to instill, but difficult to take out only one drop and you get 2 drops, please circle the number with a double circle. Entry example: A and B are both relatively difficult to instill, C is very easy to instill, D is even more easy to instill, but two drops are instilled.

and Nitten (42.7 mg) had significantly lower values.

3.3. Measurement of nozzle inner diameter

The nozzle inner diameter of each eye drop container used in this experiment was measured (Figure 4, bar graph). The nozzle inner diameter of Hyalein was 1.69 mm, whereas that of the generic drugs ranged from 0.95 to 2.03 mm (Figure 4). In particular, Tearbalance (1.06 mm), Wakamoto (1.18 mm), and Nitten PF (0.95 mm) had significantly lower values, whereas Kyorin (2.03 mm) had a significantly higher nozzle inner diameter.

3.4. Measurement of eye drop container thickness

The thickness of each eye drop container used in this experiment was measured (Figure 4, line graph). The thickness of Hyalein was 0.84 mm, whereas that of the generic drugs ranged from 0.45 to 1.18 mm (Figure 4). In particular, thickness of Eyecare (0.57 mm), Kyorin (0.53 mm), Pfizer (0.49 mm), Wakamoto (0.45 mm), TS (0.52 mm), Towa (0.46 mm) and Nitten (0.64 mm) were significantly lower. In contrast, thickness of Tearbalance (1.18 mm) and Hyalonsan (1.15 mm) were significantly higher.

3.5. Measurement of squeeze force with HapLog® and DF

The results of the average maximum squeeze force of 12 eye drops using HapLog® and DF are shown in Figure 5. For measurements using HapLog®, the average squeeze force for Hyalein was 10.5 N, whereas that for the generic drugs ranged from 14.7 to 44.3 N (Figure 5). In particular, Eyecare (34.0 N), Kyorin (35.4 N), and Nitten PF (44.3 N) showed significantly higher values. In contrast, for DF measurements, the average squeeze force for Hyalein was 12.2 N, and that of the generic drugs ranged from 8.2 to 25.0 N. In particular, Kyorin (20.8 N) and Nitten PF (25.0 N) showed significantly higher values.

3.6. Questionnaire using a 6-point scale of the "feeling of use" of various eye drops

The relationship between the ratings and the squeeze force measured using HapLog® is shown in Figure 6. Hyalein was rated 6.0 points because it was very easy to instill, whereas the evaluation of the generic drugs ranged from 1.4 to 5.5 points. In particular, Kyorin (2.3 points) and Nitten PF (1.4 points) had significantly

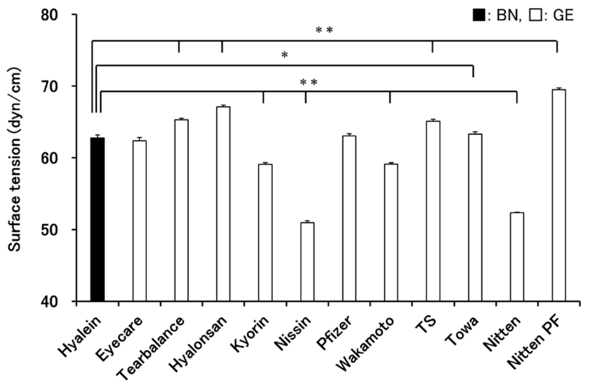


**Figure 2. Surface tension measurement of various eye drops preparations ($n$ = 6).** BN: brand-name drug, GE: generic drug, * $p < 0.05$, ** $p < 0.01$ (*vs* Hyalein, *Dunnett*-test)

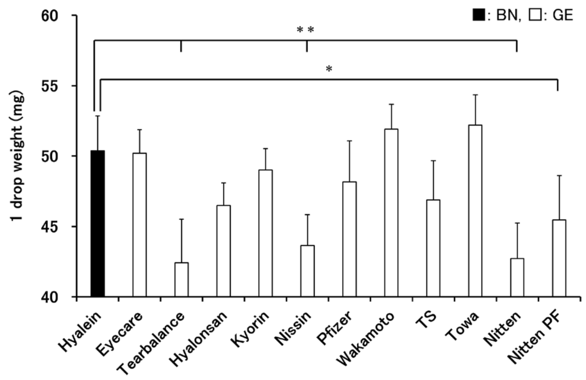


**Figure 3. One drop weight measurement of various eye drops preparations ($n$ = 6).** BN: brand-name drug, GE: generic drug, * $p < 0.05$, ** $p < 0.01$ (*vs* Hyalein, *Dunnett*-test)

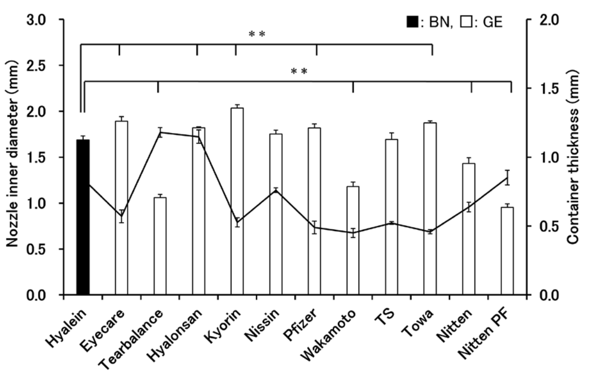


**Figure 4. Nozzle inner diameter (Bar graph) and container thickness (line graph) measurement of various eye drops preparations ($n$ = 6).** BN: brand-name drug, GE: generic drug, ** $p < 0.01$ (*vs* Hyalein, *Dunnett*-test).

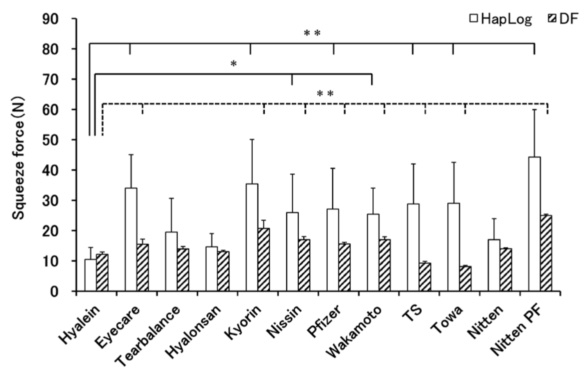


**Figure 5. Squeeze force of various eye drops measured using Haplog® and DF ($n$ = 6).** DF: digital force gauge, * $p < 0.05$, ** $p < 0.01$ (*vs* Hyalein, *Dunnett*-test)

lower ratings for ease of instillation. The correlation coefficient was calculated from the approximate curve and showed a strong negative correlation (y = – 0.1357x + 7.6511, $R^2$ = 0.8937).

3.7. Questionnaire survey using a continuous scale of the "feeling of use" of various eye drops

The relationship between the scale and squeeze force measured using HapLog® is shown in Figure 7. Hyalein was evaluated at 66.8 mm, whereas the evaluation of the generic drugs ranged from – 68.4 mm to 66.1 mm. In particular, Kyorin (– 35.3 mm) and Nitten PF (– 68.4 mm) were significantly underrated. The correlation coefficient was calculated from the approximate curve and showed a strong negative correlation (y = – 3.9804x + 120.77, $R^2$ = 0.9095).

**4. Discussion**

Kawashima studied the difference in drop volume of various eye drops, and suggested that drop volume may be influenced by the characteristics of eye drops, the shape of eye drop container, and the application technique of eye drops (*11*). The characteristics of

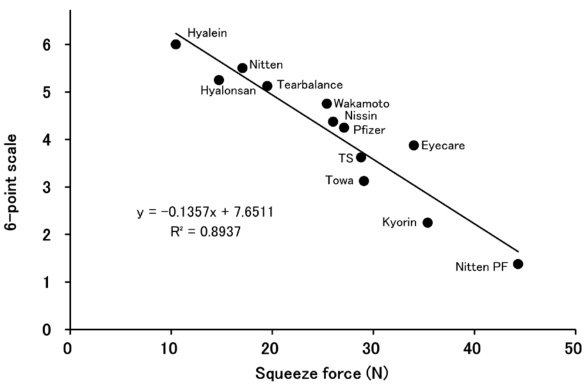


**Figure 6. Correlation between 6-point scale and squeeze force of various eye drops measured using Haplog® (*n* = 8).**

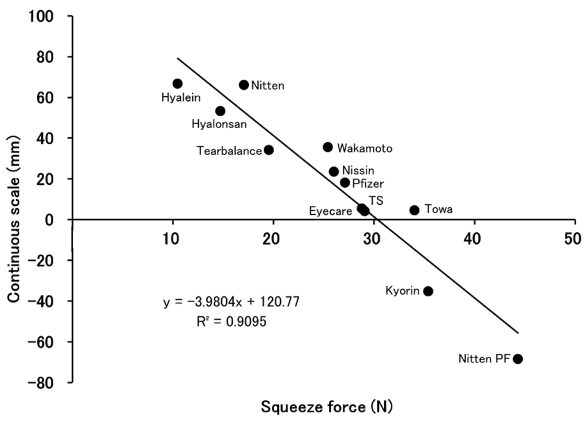


**Figure 7. Correlation between continuous scale and squeeze force of various eye drops measured using Haplog® (*n* = 8).**

ophthalmic solutions are determined by the liquidity of the ophthalmic solution, surface tension, and viscosity, and the amount of drops varies with the product, even if an ophthalmic container with the same shape is used. Kawashima also found that eye drops with high surface tension have a large drop volume, whereas drops with low surface tension have a small drop volume (*11*). Consistent with this, we found that the surface tension of Hyalein (1.69 mm) and Nissin (1.75 mm), which have similar nozzle inner diameters, was 62.8 dyn/cm and 51.0 dyn/cm, respectively, and the drop volume was 50.4 mg and 43.7 mg, respectively (Figures 2-4).

Furthermore, Wada *et al.* reported that surfactants, such as benzalkonium chloride, affect the surface tension of eye drops and that surface tension decreases in a concentration-dependent manner (*6*). Among the preparations used in the present study, Hyalein (62.8 dyn/cm), Nissin (51.0 dyn/cm), and Wakamoto (59.1 dyn/cm) contain the cationic surfactant benzalkonium chloride. In addition, the ophthalmic solution Nitten (52.3 dyn/cm) contains polysorbate 80, a nonionic surfactant. Nissin, Wakamoto, and Nitten showed significantly low surface tension values, but Hyalein did not show low values despite containing benzalkonium chloride (Figure 2). This is attributed to the addition of the benzalkonium chloride preservative, propylene glycol, which has antibacterial activity (*12*). Therefore, the concentration of benzalkonium chloride may be lower than in other products. Also, Nagai *et al.* reported that benzalkonium chloride causes strong corneal epithelial damage and that polysorbate 80 has a delayed corneal epithelial wound healing effect (*13*). Based on this, products other than benzalkonium chloride-containing preparations (Hyalein, Nissin and Wakamoto) and polysorbate 80-containing preparations (Nitten) may be appropriate for long-term use in patients.

Yoshikawa and Yamada reported no significant correlation between drop volume and bottle hardness for various glaucoma eye drops (*14*). Therefore, we investigated the association between drop volume and nozzle diameter. The amounts in one drop of Tearbalance (42.2 mg), Nissin (43.7 mg), Nitten (42.7 mg), and Nitten PF (45.5 mg) were significantly lower than that of Hyalein (50.4 mg) (Figure 3). In addition, the nozzle diameter of Hyalin (1.69 mm), Tearbalance (1.06 mm), Wakamoto (1.18 mm), Nissin (1.43 mm), and Nitten PF (0.95 mm) were significantly low. Therefore, for most formulations, excluding Wakamoto (nozzle diameter 1.18 mm, drop volume 51.9 mg), the nozzle diameter and the drop volume were correlated (Figures 3 and 4).

The hardness and squeeze characteristics of each eye drop container are important not only in terms of ease of use, but also in terms of economy. Murakami *et al.* reported that the shape of the eye drop container, the material of the main body, and the hardness of the container can influence the squeeze characteristics (*15*). Similarly, the squeeze force was reported to be affected by the material and hardness of the container, whereas the drop volume is affected by the surface tension of the eye drops and the opening diameter of the nozzle tip of the container (*16*). In addition, Wada *et al.* found a strong negative correlation between the squeeze characteristic of eye drops and subjective ease of extrusion (*6*). We found that the average maximum squeeze force of each of the eye drops using HapLog® and DF was 10.5 N and 12.2 N for Hyalein, respectively, whereas Eyecare (34.0 N and 15.5 N), Kyorin (35.4 N and 20.8 N), TS (28.8 N and 9.3 N), Towa (29.1 N and 8.2 N), and Nitten PF (44.3 N and 25.0 N) showed 1.7- to 3.5-fold differences between HapLog® and DF. These differences may be due to the difference in the measurement method; HapLog® was sandwiched between the surfsce of the fingers, whereas the eye drop container was sandwiched by "points" using the DF with hemispherical urethane spherical compression jig. Moreover, the products that require high squeeze power to instill eye drops may be considered undesirable, and Kyorin and Nitten PF showed high squeeze force values. Nitten PF is a formulation that does not contain any preservative, and is available in a special eye drop container that drops a chemical solution through a membrane filter in order to prevent bacterial contamination. The drug solution may be more resistant when passing through the membrane filter compared with the hardness of the container (*17*), and may be the reason behind the high squeeze force value of Nitten PF. Therefore, when changing from other products to Nitten PF, it is necessary to inform the patient that the drug solution is more difficult to instill from the container due to absence of preservatives; in general, it is important to accurately convey the characteristics of each product to the patient.

Hyodo *et al.* investigated differences in the squeeze force required for eye drops and the time required for instillation of glaucoma eye drops, and found that the average maximum squeeze force and average drip time affected the usability of eye drops (*18,19*). Additionally, Doi *et al.* reported that Azorga® combination ophthalmic suspension (Novartis Pharma Co., Ltd., Tokyo, Japan) affects the subjective ease of use (*i.e.* feeling of use) of eye drops (*20*). Therefore, we conducted a questionnaire survey on the "feeling of use" of 12 types of eye drops using HapLog®, and found a negative correlation with the 6-point scale and the continuous scale ($R^2$ = 0.8937 and 0.9095, Pearson's correlation coefficient – 0.945359 and – 0.953684, respectively). Furthermore, the results of both scales were almost equivalent: Hyalein (6.0 and 66.8, respectively) > Nitten (5.5 and 66.1) > Hyalonsan (5.3 and 53.3) > Tearbalance (5.1 and 34.1) > Wakamoto (4.8 and 35.6) > Nissin (4.4 and 23.5) ) > Pfizer (4.3 and 18.1) > Eyecare (3.9 and 5.4) > TS (3.6 and 4.1) ≒ Towa (3.1 and 4.5) > Kyorin (2.3 and -35.3) > Nitten (1.4 and – 68.4). In particular, the evaluations for Kyorin (2.3 and – 35.3) and Nitten PF (1.4 and – 68.4) were significantly lower than that for Hyalein (6.0 and 66.8) (Figures 6 and 7). As the 6-point scale and continuous scale yielded comparable results, the squeeze force was inversely correlated with the "feeling of use" (ease of eye drops) regarding the "usability" of each preparation. Furthermore, for patients using Hyalein, it seems that generic drugs (such as Nitten, Hyalonsan and Tearbalance) with similar "feelings of use" may be recommended without any sense of incongruity.

In our study, we confirmed that the squeeze force required for instillation varies depending on the container and the patient. In addition, in regards to instillation, a greater force of the finger was required when instilling with HapLog® compared with DF. Currently, there are a wide variety of eye drops available in the market; if the pharmacist understands the "usage" differences between the brand name and the generic products, they may be able to make appropriate eye drop recommendations that meet the needs of patients that are taking medication.

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