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Clinical significance of topical instillation technique in Japanese glaucoma patients

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The clinical significance of a proper eye drop application technique was evaluated in Japanese glaucoma patients. Patients diagnosed with primary open-angle glaucoma having intraocular pressure (IOP) greater than 21 mmHg were treated with eye drops at home. In some patients, however, the topical treatment was ineffective. They returned to the hospital to receive surgical treatment. On admission, 56% of these patients had IOP greater than 21 mmHg. Patient instillation technique was evaluated based on the proximity of the eyedropper tip to the eyes, application position, eyelid closure, treatment (removal) of excess fluid, and nasolacrimal occlusion. In addition, pharmacists interviewed patients to determine the level of understanding of glaucoma, knowledge of prescribed drugs, home application technique, and sensation after application. Multivariate analysis revealed that the key factors influencing the control of IOP to less than 21 mmHg with topical medication were: application of drops in the center of the eye and removal of excessive fluid, in addition to gender and age. Proper topical application at home was dependent on the patient's understanding of the disease, knowledge of prescribed drugs, patient education on the use of drugs, the competence of the instructor, and knowledge of correct application technique. This study indicates that easily comprehensible patient education on the use of eye drops, the nature of glaucoma and the proper use of prescribed drugs is vital to improving the clinical efficacy of topical ophthalmic medication of glaucoma in adult patients.

1. Introduction

Glaucoma is a group of eye diseases that damage the optic nerve and cause some vision loss. There are several classification methods for glaucoma, depending on chamber angle and the reasons for elevated intraocular pressure (IOP). In Japan, glaucoma is classified broadly into 4 categories as follows: primary glaucoma, secondary glaucoma, developmental glaucoma, and secondary glaucoma in childhood (*Terminology and Guidelines for Glaucoma*, Japanese Ophthalmologic Society). Primary glaucoma is further divided into primary open-angle glaucoma, primary closed-angle glaucoma, and mixed glaucoma. Open-angle glaucoma is the most common type, involving slow damage to the optic nerve and gradual loss of sight. Most patients with open-angle glaucoma have an IOP greater than 21 mmHg, which is never seen in a normal eye (Sihota et al. 2005; Sowka 2005). However, some open-angle glaucoma patients have normal IOP. This type is called normal-tension glaucoma.

Treatment for glaucoma usually begins with the use of a topical selective or non-selective β-blocker or a prostaglandin analog to reduce IOP and prevent or delay progressive glaucomatous optic neuropathy (Fleming et al. 2005; Lee and Higginbotham 2005; Rouland et al. 2005). The management of glaucoma with eye drops, however, is not always effective in reducing IOP and may have adverse local or systemic effects, such as ocular irritation, allergic conjunctivitis, respiratory failure, cardiac failure, and depression (Ito 1999, Ikeda et al 2001; Lee and Higginbotham 2005). In such cases, eye care practitioners consider laser trabeculoplasty or incisional surgery the next step in the effort to lower IOP (Distelhorst and Hughes 2003). Prior to taking such steps, however, it is important to identify the reason(s) why the topical medication failed to help the patient. In principle, the efficacy of medication is dependent on the pharmacological action of the ingredients used, the concentration of the drug at the target site, and the sensitivity of the patient to the drug. Based on these considerations, several factors could be involved in topical medication as follows: Was the choice of drug appropriate? Was the dosage regimen and application technique adequate? Did the patient apply the eye drops as indicated? Improper application technique can significantly reduce pharmacological action. To a greater extent than other administration modalities (oral administration

and intravenous injection), the efficacy of topical medication can fluctuate greatly depending on the patient's application technique (Winters et al. 2001; Kapentansky 2003). The present study evaluated the clinical significance of proper eye drop application technique in Japanese glaucoma patients to determine factors influencing the control of elevated IOP by self-application of eye drops. Correct eye drop application technique was defined as follows: no contact between eyedropper and eyes, application of drop into the center of each eye (the middle of the opened conjunctival sac), eyelid closure and occlusion of nasolacrimal region, and removal of excess fluid.

2. Investigations and results

Twenty-seven Japanese glaucoma patients diagnosed with primary open-angle glaucoma and treated with pharmacotherapy within 1 year participated in the present study. Normal-tension glaucoma patients were not included. The initial treatment for all 27 was self-application with eye drops at home using a combination of a prostaglandin analogue + a β-adrenergic blocker, a prostaglandin analogue + a carbonic anhydrase inhibitor, a prostaglandin analogue + a β-adrenergic blocker + a carbonic anhydrase inhibitor, or a β-adrenergic blocker + a carbonic anhydrase inhibitor (on average, 2.2 ± 1.3 ophthalmic solutions). However, these 27 patients returned to the hospital to receive surgical treatment because the self-application was not effectively slowing the progress of glaucoma. All (27) patients had IOP greater than 21 mmHg before the initial self-application, and 20 patients (74%) participated in the evaluation of topical application technique. The remaining 7 patients declined to participate in the evaluation of application technique. Informed consent was obtained from all patients participating in this study, as approved by the institutional review board. Their IOP values were 22.7 ± 9.6 mmHg (mean $\pm$ SD, $n = 20$) in a range from 11 to 48 mmHg, and 11 patients (55%) had IOP greater than 21 mmHg. Application techniques were evaluated based on the proximity of the eyedropper tip to the eyes, application position (the middle of the opened conjunctival sac), eyelid closure and nasolacrimal occlusion for 10 s, and treatment (removal) of excessive fluid (5 technique elements). Four patients (20%) performed all 5 technique elements correctly. The other 16 patients (80%) did not. Twelve patients (60%) did not close their eyes properly, and 14 patients (70%) did not compress the nasolacrimal region after topical application (Fig. 1).

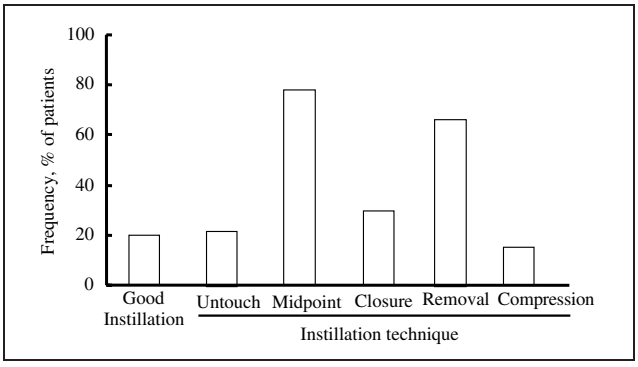

Fig. 1: Observation of application techniques. Good application – all good application techniques as indicated; Non-contact – no contact of eyedropper tip to the eye; Midpoint – application in the center; Closure – eye closure for at least 10 s after application; Compression – compression of lacrimal region for at least 10 s after application; Removal – removal of excess fluid

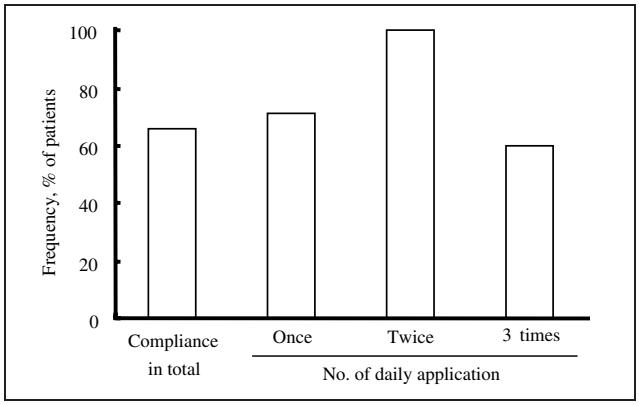

Fig. 2: Survey for compliance with treatment regimen

Subsequently, pharmacists interviewed the patients to assess their understanding of glaucoma, knowledge of the prescribed medications, knowledge about application method, and sensation after application by using a checklist. All 27 patients participated in these interviews. Twenty-three patients (85%) did have adequate knowledge of glaucoma, of which 19 patients (70%) obtained the information from their physicians. Sixteen patients (59%) obtained their knowledge of medications from physicians, and 5 patients (19%) from pharmacists prior to topical medication. Most patients (96%) did know the dosing regimen (the number of drops used and administration intervals) for their eye drops. Ten patients (37%) did not follow the regimen at home, though 27 patients with a regimen of twice daily application performed as indicated by the physician (Fig. 2). Seventeen patients (63%) sometimes forgot to apply the eye drops, especially during the daytime: daytime (10 patients, 37%) > morning (5 patients, 19%) > evening = bed time (3 patients, 11%). Eleven patients (41%) answered that they washed their hands before using the eye drops, and 23 patients (85%) applied one drop of ophthalmic solution. When patients used multiple eye drop preparations (2.2 ± 1.3 ophthalmic solutions), 18 patients (67%) distinguished them by the color of the dropper cap. Three patients (11%) used the shape of eyedroppers. Twenty-three patients (85%) using multiple preparations applied the solutions in a predetermined order. A 5 min interval is suggested for multiple eye drop preparations at Hiroshima University Hospital, and 17 patients (63%) applied the next preparation after more than 3 mins, whereas 3 patients (11%) did so within 1 min (Fig. 3). Fifteen patients (56%) closed their eyes properly and 9 patients (33%) compressed the nasolacrimal region for more

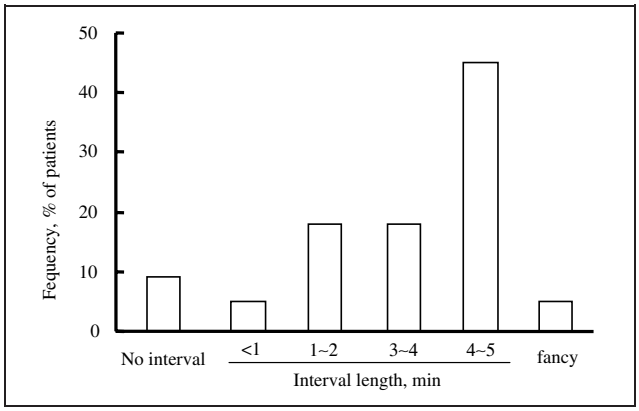

Fig. 3: Survey for interval length when multiple ophthalmic preparations were applied

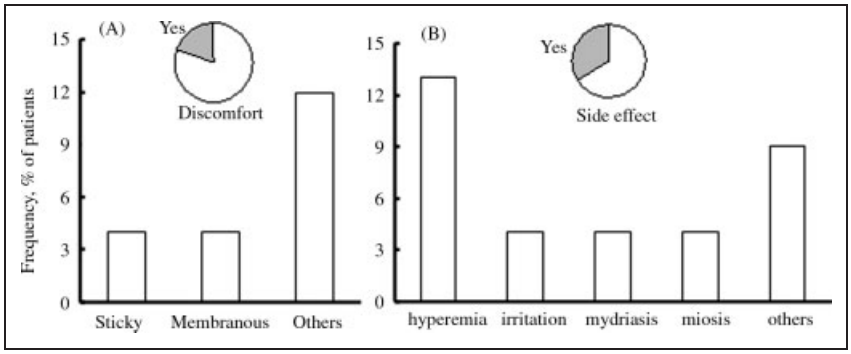

Fig 4:
Survey for sensations (A) and side effects (B)

than 10 s after application. Ten patients (37%) who used a β-adrenergic blocker preparation reported a bitter taste after application of the eye drops. In total, 6 patients (22%) experienced uncomfortable sensations in the eyes, including stickiness (1 patient with 0.5% timolol gel), a membranous sense (1 patient out of 22 patients with 0.005% latanoprost), or ocular irritation with latanoprost (Fig. 4). Side effects were reported by 30% (8 patients) of the patients, including inflammation of the eye (4 patients with latanoprost), mydriasis/miosis (3 patients), and systemic side effects (1 patient) with 0.25% nipradilol, respectively. Side effects assessed by patients as unacceptable were decreased vision (74%, 20 patients out of 27), black pigmentation (formation of black rings under eyes) (52%), hyperemia of the eyes (37%), intension of eyelash (26%), and ocular irritation (19%). Side effects patients were willing to tolerat were ocular irritation (78%), intension of eyelash (67%), hyperemia of the eyes (59%), black pigmentation (44%), and decrease in vision (19%).

Multivariate analysis revealed that the factors (having a range score of >1.5) in distinguishing IOP values more or less than 21 mmHg in glaucoma patients were: proper application position (range score: 1.90) and removal of excess fluid (range score: 2.82), in addition to gender (male $<$ female) (range score: 1.93) and age (>65) (range score: 1.91) (Table). The determining factors for proper application technique were understanding of the disease (range score: 2.77), knowledge of medications (2.87), patient education on the use of drugs (1.72), instructor competence (5.89), and knowledge of application technique (1.78).

As described in the introduction, the application technique is one of the important factors in achieving effective pharmacological action with eye drops. In the present study, 15 glaucoma patients out of 27 had IOP greater than 21 mmHg on admission to hospital, irrespective of self-application with eye drops. This fact suggests that topical medication is not effective if the drug is not applied properly. In the present study, observation revealed that only 30% of patients compressed the nasolacrimal region after application (6 patients out of 20) by observation. This figure rose to 33% (9 patients out of 27) by questionnaire survey. The percentage of patients that closed their eyes properly was 35% (7 patients out of 20) by observation and 56% (15 patients out of 27) by questionnaire survey.

Table: Factors and range scores in distinguishing IOP values evaluated by multivariate analysis

Factors	Range Score
Instructor competence	5.887
Knowledge of medications	2.868
Removal of overflowed eye drops	2.819
Understanding of the disease	2.770
Gender	1.935
Age	1.909
Adequate instillation potition	1.902
Knowledge of instillation technique	1.780
Patient education on the use of drugs	1.716
Eyelid closure	0.473
Touch of eyedropper tip to eyes	0.151
Compression of lacrimal region	0.037
Eye drops	0.007

3. Discussion

Tear fluid undergoes four processes: production by the lacrimal gland, distribution by blinking, evaporation from the ocular surface and drainage through the nasolacrimal duct (Tsubota 1998). As with tears, ophthalmic solution applied topically would also be distributed on the ocular surface by blinking, evaporated partly from the surface and drained partly through the nasolacrimal duct. Therefore, the compression of the nasolacrimal region followed by eye closure after topical application can prevent the drainage of ophthalmic solution from the ocular surface and thereby increase retention of the drug on the ocular surface.

In the present study, 60–70% of patients during our observation failed to compress the nasolacrimal region and more than half perceived a bitter taste after topical application of β-adrenergic blockers, indicating the elimination of ophthalmic solution into the nasolacrimal duct. These facts suggest that easily comprehensible and detailed patient training in topical application method is necessary to improve the clinical efficacy of topical medication.

In the interviews, 23 patients (85%) out of 27 reported that they did understand open-angle glaucoma, which means that 4 patients did not know the name of their own eye disease. However, in general, physicians do inform patients about the disease before they start the therapy at least in Hiroshima University Hospital. As well, 8 patients (30%) reported that they received no information from the pharmacist regarding their medicines. These facts indicate that about 15–30% of patients in the present study could not understand the explanations they received from their ophthalmologists or pharmacists. A more careful and simpler explanation by ophthalmologists or pharmacists could improve the patients' knowledge. Most patients (96%) did know the daily dosage regimen for the medication they were using, but 38% reported that they did not comply fully to the regimen at home. The reasons for this noncompliance are not clear. In general, it seems that eye drops requiring less frequent administration are preferable to those that require multiple daily dosing. Unexpectedly, however, compliance with regimens requiring eye drops

twice daily (morning and evening) was higher than that for once-daily application (100% vs. 71%). Eye drops for once-daily application contain polymer compounds such as gellan gum and methylcellulose for timed release, and these tend to make the ocular surface sticky. They also reduce visual acuity for about 5 min, possibly resulting in greater perceived distress or inconvenience. It is important to take the patient's lifestyle into consideration when determining the most appropriate dosage regimen or ophthalmic solution.

When a patient uses multiple ophthalmic preparations, the application interval and the order of application are important. When multiple preparations are applied consecutively without a sufficient time interval, pharmacological effects are reduced due to drainage from the conjunctival sac and ocular surface. It is difficult to determine theoretically an appropriate application interval for each ophthalmic preparation, because of the different physicochemical properties of the drugs and ophthalmic preparations. At Hiroshima University Hospital, in general, a 5 min time interval is recommended for multiple applications. We counseled hospitalized patients regarding proper intervals of administration. In the present study, an interval of more than 3 min was observed in 63% of the patients on self-report. The shorter interval could be the cause of the insufficient pharmacological effect.

In determining the order of application for multiple preparations, in general, the most viscous solution is applied last. However, limited information is available on how to determine the most effective sequence of application. Actually, 24 patients (89%) out of 27 used multiple ophthalmic preparations in a self-determined order. Detailed investigation is necessary to determine the proper theoretical order for various sets of eye drops. Also, eye drops were found to be distinguished primarily (21 patients out of 27) by their cap colors or the shape of the eyedropper. Thus, a statement regarding eye dropper cap color would be vital drug information.

Six patients (22%) out of 27 reported discomfort due to topical medication. In particular, they complained of blurred vision and ocular irritation due to the long-acting (-blocker timolol, which causes blurred vision lasting for about 5 min. Systemic side effects due to topical medication were observed in 9 patients out of 27. All 9 patients failed to compress the nasolacrimal region after application of the eye drops. It is important to let patients know the importance of compressing the nasolacrimal region to avoid systemic side effects. Prostaglandin side effects were the following in descending order of frequency: ocular irritation, intension of eyelash, hyperemia of eyes, eyelid pigmentation, and decrease in vision. Among these side effects, the decrease in vision and the eyelid pigmentation were considered by patients to be unacceptable. Appropriate advance instruction is necessary when patients, especially elderly patients, use drugs that cause such side effects (Burns and Mulley 1992; Winfield et al. 1990).

Statistical analysis revealed that the factors influencing control of IOP to less than 21 mmHg with topical medication were application of drops in the center and removal of excess fluid, by which side effects such as intension of eyelash, change in eyelid pigmentation, and skin irritation can be reduced (Iwaki et al. 1991). This analysis indicated that proper application technique was necessary to control IOP. The gender (female > male) and age (>65 years old) of patients also affected IOP values. Women may apply eye drops more carefully, and elderly patients with more than 10 years history of glaucoma have more experience with topical application. Proper topical application at home, though based on self-report, appears to depend on understanding of the disease, knowledge of medications, patient education regarding the use of drugs, instructor competence, and knowledge of the correct application technique. These parameters relating to patient understanding also improved compliance with the treatment regimen. Our previous study also suggested that the factors influencing patients' adherence were the number of ophthalmic solution, age, the taste of the ophthalmic solution, administration intervals, the number of drops and washing hands before applying the ophthalmic solution, though the subject numbers were small (Ikeda et al. 2001).

In conclusion, the clinical significance of proper application technique was evaluated in Japanese glaucoma patients to find factors influencing pharmacological effects. Although the number of subjects was small, the importance of proper topical application technique emerged clearly. This study suggests that easily comprehensible patient training in the use of eye drops and education regarding glaucoma and medicines are important to the clinical efficacy of topical ophthalmic medication of glaucoma in adult patients.

4. Experimental

4.1. Patients

Twenty-seven Japanese patients (16 males, 11 females) with open-angle glaucoma were enrolled in this study, and 20 patients participated in the evaluation of application technique. Informed consent was obtained before the measurements of IOP from all patients. IOP measurements were performed using Goldmann applanation tonometry at 9 AM by ophthalmologists. The patients had been performing self-application at home with clinically available eye drops, including β-adrenergic blockers, epinephrine, cholinergics, carbonic anhydrase inhibitors, and prostaglandins (Lee and Higginbotham 2005). Subjects ranged from 32 to 76 (62.2 ± 2.9) years in age. On admission to the hospital, the measured IOP of patients was 22.7 ± 9.6 (11–48) mmHg, and 11 of the 20 patients that participated in the evaluation of application technique had IOP greater than 21 mmHg.

4.2. Observation of topical instillation technique

After obtaining informed consent in an interview, pharmacists directly observed the application technique of 20 patients before offering patient training in the use of eye drops. Patients applied a drop of benzalkonium chloride free test solution using a 5-mL eyedropper, and the technique was evaluated using the following 5 technique elements: Did the tip of the eyedropper contact the eyes during application? Was the drop applied to the correct part of the eye (the middle of the opened conjunctival sac)? Did the patient keep the eyelid closed and compress the nasolacrimal region for at least 10 s after application? Did the patient remove excess fluid to reduce side effects? Multivariate analysis was performed with the IOP value of 21 mmHg as a criterion variable. Explanatory variables used were age, gender, and the above 5 technique elements (contact or non-contact of eyedropper tip, instillation in the center, eyelid closure, removal of excess fluid, and compression of nasolacrimal region).

4.3. Interview by pharmacists

Pharmacists interviewed each patient to assess understanding of glaucoma (disease, demonstration), knowledge of drugs (drugs, dosage, dose, interval), application method for eye drops (non-contact, midpoint, closure, removal, compression), and sensations due to the medication (hyperemia, irritation, mydriasis, miosis, eyelash) by using a checklist.

4.4. Statistical analysis with multivariate analysis

Multivariate analysis by using HALWIN® was performed to evaluate the clinical significance of proper eye drop application technique in Japanese glaucoma patients to determine factors influencing the control of elevated IOP through the self-application of eye drops. Correct eye drop application technique was defined as follows: non-contact of eyedropper tip to the eyes, placement of drop into the center of eyes, eyelid closure and occlusion of nasolacrimal region, and removal of excess fluid as described in drug package inserts. Values with a range score of 1.5 or more were considered influencing factors.

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