# **Original article**

# The effect of the Thai "Eye Drop Guide" on success rate of eye drop self-instillation by glaucoma patients

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**Background:** Noncompliance can mislead clinicians regarding the efficacy of therapy and result in more aggressive, but inappropriate treatment. Improper techniques used for eye drop instillation frequently occurs in chronic glaucoma patients. The Thai Eye Drop Guide (EDG) device has been developed to ensure precise instillation. However, whether the EDG is more effective than the traditional technique when careful instructions for both techniques are given is still unknown.

*Objective:* To compare success rates of eye drop self-instillation by chronic glaucoma patients using a traditional technique and the EDG when careful instructions for both are given.

*Methods:* Fifty-nine chronic glaucoma patients were instructed to instill eye drops using the EDG or a traditional technique in a randomized sequence. A two week practice period was assigned before groups were crossed-over. The instillation performance was VDO recorded after each practice period. Three criteria of success: time taken to instill an eye drop into the eye; instillation of only one drop; and without the bottle tip touching lids, lashes, periocular tissues, or the other hand, were scored by three independent readers from video-records. The readers were blinded to the sequence to which the patients were randomized.

*Results:* There were no significant differences in success rates between the EDG and traditional technique (61.0% and 66.1% respectively, p = 0.607) and the number of drops dispensed per application (median of 1 drop in both groups, p = 0.89). The time taken to instill eye drops with the EDG was significantly longer than using the traditional technique (median of 19 and 9 s respectively, p < 0.001). Older age (p = 0.049, OR 4.23) and more education (p = 0.025, OR 0.19) were found to be significantly associated with failure of the EDG.

*Conclusion:* EDG is not more effective than a traditional technique in terms of improving dispensing accuracy and decreasing the drops dispensed per application even when careful instructions are given. The results suggest that, if good instructions are provided, experienced glaucoma patients can improve their eye drop instillation performance.

Keywords: Compliance, drop administration, eye drop guide, glaucoma, self-instillation

The purpose of glaucoma treatment, most commonly with antiglaucoma eye drops, is to lower the intraocular pressure to retard or stop further vision loss. The intentional or accidental failure to take drops (noncompliance) is a major problem in glaucoma treatment. Noncompliance can be confused with lack of efficacy and lead to more aggressive treatment that will increase health care costs [1, 2]. For eye drops, noncompliance can be in the form of failure to take medication, improper timing of medication, taking the wrong medication, or taking excessive medication, in addition to improper techniques of administration. The common mistakes in eye drop administration observed in glaucoma patients includes an inability to instill a drop into the eye, instilling more than one drop, and touching the bottle tip to the eye or periocular tissues [3-8]. Incorrect techniques may increase health care costs and harm the eyes, e.g. by contamination, conjunctival congestion, conjunctival erosion, and episcleritis [9].

Various forms of aligning devices to improve accuracy of eye drop instillation have been developed [10-13]. None has been tested objectively for accuracy or efficacy. The Eye Drop Guide (EDG) is the first device developed in Thailand (Patent number 6555,

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Mahidol University, 2 Sep 2011). Its purpose is to ensure precise instillation and prevent the bottle tip from touching the eye. It was made of lightweight plastic (chemically inert thermoplastic polystyrene) in a shape and size of a regular eye wash cup. The rim is curved to fit the orbit. One of the disadvantages of the EDG is that it was designed to fit the largest eye drop bottle available (15 ml). However, most glaucoma eye drop bottles are 2.5, 3, or 5 ml and may not closely fit the device. If the patients' hands are not steady, the tips may sway when applying the eye drops. Another disadvantage it is available in only one size and may not fit properly in the orbit of some patients. Furthermore the EDG also requires skill and practice in order for patients to self-instill eye drops successfully.

Although instillation problems are well documented, clinicians often neglect these problems and assume that chronic glaucoma patients understand how to self-instill eye drops correctly. Whether the EDG is more effective than the traditional technique (without a device) remains hitherto unknown. In this study we compared success rates of eye drop selfinstillation using the EDG and a traditional technique in patients with chronic glaucoma.

#### Materials and methods

A randomized cross-over design was used to eliminate the carry over effect (practice effect). Participants perform better over time because of practice and perform best with the most recently used technique. The study was conducted at the Faculty of Medicine, Siriraj Hospital, Mahidol University. The study was approved by the institutional review board [SI 487/2012 (EC4)] and is registered by Clinical Trials.gov (NCT01704248). Written informed consent was obtained from all participants.

# Inclusion and exclusion criteria

Patients were enrolled from the out-patient clinic by the primary investigator who did not attend any of the participants. The patients were eligible for the study when they met all 3 criteria:  $age \ge 18$  years; diagnosed with chronic glaucoma  $\ge 3$  months; and regularly selfadministering antiglaucoma eye drops. Criteria for exclusion were unwillingness to participate; allergy to artificial tears; perioperative status; visual loss from diseases other than glaucoma; ophthalmic conditions that affect the eye drop instillation e.g. nystagmus, ptosis, exophthalmos, and general conditions that affect the patient's adherence to the protocol, e.g. dementia, psychosis, rheumatoid arthritis, neurological conditions resulting in tremor or paralysis.

#### Baseline evaluation and video-record setting

Baseline characteristics were collected from medical records and interviews. Two digital cameras (Canon EOS 550D) were set to record the performance of participants in 2 different angles at 0.5–1 meter from the eyes. It started when participants received the uncapped bottle in their dominant hands. The 3 ml bottle of artificial tears contained, 0.5% carboxymethyl cellulose Na (Cellufresh MD, Allergan, Irvine, USA). It was used for the study. The participants were asked to instill the artificial tears into the eye using their usual technique, as they would normally do at home. The study eye was the eye with worst sight based on best corrected visual acuity (BCVA). If the BCVA in both eyes was equal the mean deviation score (MD) from the latest visual field test was used to define the eye with worst sight. This was done to make the participants familiar with the process and atmosphere of being recorded. In the study room, there was an examination bed, 3 different sizes of chairs, a table, mirror, a small standing surgical lamp, and a hand wash sink.

#### Randomization

The list of random numbers was computergenerated by a statistician not involved in other parts of the study. The opaque, sealed envelope containing the assigned treatment sequence was drawn by a primary investigator after baseline video recording.

# Procedures

All participants received training with both techniques and were randomly assigned to start with either the EDG (group 1) or the traditional technique (group 2). Each technique was carefully considered following the same instruction manual by the primary investigator, but allowing adjustments in details to serve each participant better. The participants would practice until confident in the techniques, to which they were randomized. The participants then were assigned to practice instilling eye drops in both eyes with the assigned technique at home for 2 weeks and keep the diary of date, time, and number of bottles used with the technique used in each eye. The participants were assigned to practice with the study eye drops and then their own medications. The evaluation session was the groups were crossed over. To be able to see the eye drops when instilling with the EDG a  $1.5 \times 3$  cm. window was made on the device (**Figure 1**). The video photographers recorded the participants' performance with the device through this window (**Figure 2**).



Figure 1. Eye Drop Guide modification for video-record



Figure 2. Video-record of the instillation performance with EDG

## Primary and secondary outcomes

Primary outcome was between group comparison of success rates, defined by the three criteria: time taken to instill an eye drop into the eye; instillation of only one drop; and without the bottle tip touching lids, lashes, periocular tissues, or the other hand.

Secondary outcomes included (1) comparison of the number of drops dispensed per application, (2) comparison of time needed to successfully instill eye drops (measured in seconds from the point when the participants had an uncapped bottle in hand until they believe one drop is successfully instilled into the eye), and (3) factors associated with failure of selfinstillation with the EDG.

#### Sample size estimation

The sample size was calculated based on success rates of eye drop self-instillation; 33.8%–80% in previous studies [3-8]. We estimated success rates of the traditional technique and the EDG to be 60% and 80% respectively. A sample size of 52 pairs will have 80% power to detect a difference in proportion of 0.200 when the proportion of discordant pairs is expected to be 0.300 using McNemar's test of equality of paired proportions with a 0.050 two-sided significance level. We increased the sample size to 64 pairs to compensate for 20% drop-out and possible video tape retrieval problems.

## Statistical analysis

The VDO records of both techniques were presented to the readers together after all the recordings were done. The readers scored the participants' performance independently and without knowing the names, the disease status, or the randomized sequence of the participants.

All analyses were performed using PASW Statistics 18 (SPSS Inc, Chicago, IL, USA). The continuous data were summarized by the mean ( $\pm$  standard deviation) or median (interquartile range) where appropriate. The categorical data were summarized by the percentage of individuals falling into each category.

Success rates comparison between 2 techniques was analyzed following this order: (a) carry-over effect was analyzed by the Pearson's chi-square test. (b) Success rate comparison was analyzed using McNemar's test. If there was no carry-over effect, data from 2 sequences were combined and analyzed using McNemar's test. In case of a carry-over effect, analysis was preformed separately for each treatment sequence.

Wilcoxon signed-rank tests were used to compare the "drops dispensed per application" and "time to instill drops" between techniques. Binary logistic regression was used to analyze the factors associated with failure of eye drop instillation.

#### Results

#### **Baseline** characteristics

Sixty-four patients with various forms of glaucoma were recruited. By our definition of success; 26 of 64 participants succeeded in eye drop instillation using their usual techniques with a mean (SD) of 1.38 (0.67) drops per application. Five participants (2 from group I and 3 from group II) withdrew from the study before the first evaluation visit at week 2. One participant was scheduled for glaucoma surgery, three withdrew because of travelling inconvenience, and one because of allergic reaction to the artificial tears used in the study. A total of 59 participants completed the entire study: their baseline characteristics were summarized in Table 1. There were no differences in baseline characteristics between the 2 randomized groups. Most of the participants had good visual function. The overall median MD was -5.14 (mild visual field defect) and median BCVA was around 20/40 (near normal vision) in the study eyes. None had visual acuity in a better eye of less than 20/200 (severe vision loss) regardless of etiology of visual impairment. Seven participants (4 from group I and 3 from group II) had severe visual impairment (LogMAR VA  $\geq$ 1) and 14 participants (8 from group I and 6 from group II) had profound visual field loss (MD  $\leq$ -15) in the study eyes. More than 85% (51/59) had used glaucoma medications for >1 year. Almost half of the participants (26/59) had recently been using only 1 medication to control their disease.

## Effect of the Eye Drop Guide

The success rates of each technique in each group are summarized in **Table 2**. A carry over effect with either technique was not found (Fisher's exact P = 0.717). The success rates for eye drops instillation for EDG technique and the traditional technique were 61% (36/59) and 66.1% (39/59) respectively. There was no significant difference in success rates between the two techniques (McNemar's P = 0.607). The number of participants that could not instill the first drop into the eye was almost double with the EDG (23 versus 12). A portion of participants were eventually unable to instill one whole drop into the eye; 9 (15%) and 5 (8%) with the EDG and the traditional technique respectively. Thirteen participants contaminated the bottle tips with the eyes or periocular tissues when instilling with the traditional technique. Although the EDG prevented the bottle tip from touching the eye, in 7 participants the drops were instilled into the device before dropped onto the eye. The number of drops dispensed per application was not significantly different between two groups, P = 0.89. The time used to instill eye drops with the EDG was significantly longer than with the traditional technique, *p* < 0.001 (**Table 3**).

## Risk factors analysis

Univariate and multivariate analyses of risk factors associated with failure of instillation with EDG are summarized in **Table 4**. The variables included in multivariate analysis were variables that were statistically significant in univariate analysis with P 0.2 and variables that were found to be significant in the previous studies i.e. female sex, age  $\geq$ 70 years, less than high school education, lower level of visual acuity, and lower visual field score.

	GroupI	GroupII	
No. of participants	30	29	
Mean age (y)	70.23 (±7.76)	66.69 (±10.83)	
Female gender	14 (46.67%)	16(55.17%)	
LogMAR BCVA*	0.3 (IQR 0.6)	0.3 (IQR 0.3)	
MD scores*	-4.90 (IQR 15.56)	-5.14 (IQR 8.41)	
<high education<="" school="" td=""><td>14 (46.67%)</td><td>12(41.38%)</td></high>	14 (46.67%)	12(41.38%)	
Duration of glaucoma (y)*	6.1 (±5.96)	6.34 (±4.19)	
Mean no. of medications*	1.63 (±0.66)	1.89 (±0.84)	
Sitting or standing position	19(63.33%)	18(62.07%)	
Same eye-hand	22(73.3%)	18(62.1%)	

Table 1. Baseline characteristics

\* = Characteristics of the study eye, LogMAR = logarithm of the minimum angle of resolution, BCVA = best corrected visual acuity, MD = perimetric mean deviation, Same eye-hand = same side of the study eye and the hand holding the bottle

Group (sequence)	A+B+	A+B–	<b>A</b> – <b>B</b> +	A-B-	Total
I (AB)	13	4	9	4	30
II (BA)	13	6	4	6	29

Table 2. Summary of success rates in group I and group II

A = Eye Drop Guide technique, B = Traditional technique

Table 3. Comparison of "Drops dispense per application" and "Time to instill drops"

	Eye Drop Guide		Traditional technique		Р
	Median	IQR	Median	IQR	
Drops per application (drops)	1	1–2	1	1–1	0.89
Time to instill drips (seconds)	19	12–30	9	6–15	<0.001

\*Wilcoxon signed-rank test

Table 4. Risk factors associated with failure of the EDG technique\*

	Univar	Univariate analysis		Multivariate analysis		
	P	Crude OR	Р	OR	95% CI of OR	
Sex: Female	0.487	1.45	0.412	1.68	0.49–5.85	
Age≥70 y	0.253	1.88	0.049	4.23	1.01-17.82	
Education < high school	0.096	0.39	0.025	0.19	0.04-0.81	
$LogMAR BCVA \ge 1$	0.823	1.20	0.389	2.89	0.26-32.34	
MD scores $\leq -15$	0.364	0.55	0.223	0.31	0.05-2.03	
Glaucoma duration < 1 y	0.926	0.93				
1 Glaucoma medication	0.642	1.28				
Sitting / standing position	0.815	0.88				
Same eye-hand	0.423	1.60				
Practice frequency $\leq 28$	0.018	5.87	0.071	5.22	0.87–31.29	

\*Binary logistic regression, LogMAR = logarithm of the minimum angle of resolution, BCVA = best corrected visual acuity, MD = perimetric mean deviation, Same eye-hand = same side of the study eye and the hand holding the bottle, Practice frequency = total number of instillations with EDG collected from patient diary

In multivariate analysis, female sex and older age were found to be significantly associated with failure of the traditional technique (P = 0.030 and 0.035 respectively). For the EDG, older age (P = 0.049, OR 4.23) and more education (P = 0.025, OR 0.19) were found to be significantly associated with failure. The practice frequency of  $\leq 28$  times was significantly associated with failure in univariate analysis (P = 0.018). However, in multivariate analysis, it was not significant (P = 0.071). No association of the frequency of practice with age or education level was observed.

#### Discussion

Various types of aligning devices have been developed to aid the eye drop self-instillation. This is the first study that objectively assessed the efficacy of the aligning device using video-records. Previous studies that video-recorded the performance of experienced glaucoma patients, evaluated their usual instillation technique. They have reported a success rate of 31% and 39% with the 2.5 ml and 5 ml bottle respectively [5-14]. Using the same triple criteria of success, the success rate of patient's usual technique of 41% in our study was consistent with previous studies. Although the EDG could improve the success rates to 61% it is not more effective than the traditional technique. When careful instruction regarding the instillation techniques was given and adapted to be suitable for each individual, the success rates were not different between the two techniques. The success rates for the EDG were substantially lower than we had expected. We had expected that the EDG would help in aligning the bottle directly above the eye, but a number of patients could not handle the device properly. As a result, 23 patients could not instill the first drop into the eye with the EDG and 17 of 23 patients administered multiple eye drops. The difficulties with the EDG that we observed were that participants could not position it properly over the eye or did not tilt their heads far back enough to allow the eye drops to enter the orbit. A few participants compressed the eye and forced the lids closed. We also observed difficulty in handling the bottle and device simultaneously; especially in older participants. The 3 ml artificial tears used in the study was not a close fit to the EDG so that the bottles were not aligned in some cases. As a consequence, 7 participants contaminated the eye drops by instilling them directly into the devices. Another consequence was that the first drop was not instilled into the eye or the participants administered multiple eye drops. We believe that if the bottle was tightly fitted to the device the difficulties in handling and misalignment would be eliminated and the success rate of EDG would be improved.

The numbers of drops dispensed per application were not different between the two groups. Although the number of participants that instilled multiple drops was almost double with the EDG, the participants whose first drop missed the eye used more drops when they were instilled with the traditional technique (23 participants instilled 2–3 drops with EDG and 12 participants instilled 2–10 drops with the traditional technique). This was probably because the EDG forced the drops to fall close to, if not into, the eye and the participants did not have to move the bottle around to get eye drops into the eye.

The time to instill drops until the participants believed one drop was successfully instilled into the eye, was significantly longer using the EDG. If more than one medication was prescribed, the difference in time to instill all drops is expected to be even greater. Therefore, if the device is not considerably more effective than the traditional technique it is unlikely that the participants will prefer to use the device. Our results suggested that participants of female sex and older age were less likely to succeed with the traditional technique. Older age and more education were found to be a predictor of failure with the EDG. Older age and female sex was found to be associated with failure of eye drop instillation in previous studies [5, 14, 15]. By contrast, different results associated with educational level was observed in a multicenter study [3]. No association of instillation performance was observed with visual impairment or severe visual field loss, although an association has been suggested in previous study [16]. Our contrasting results may be the result of the greater number of participants with good visual function participating in our study.

#### Conclusion

The limitations of our study included that we had expected a higher success rate for the EDG technique, which lead to decreased power and increased possibility of a type II error (false negative) for the study. The use of a single session VDO recording at each step may not have reflected the actual performance. Moreover, the presence of cameras and investigators may have influenced the performance (improved or worsened) of the participants.

In summary, the EDG is not more effective than the traditional technique given careful instruction, in terms of improving dispensing accuracy and decreasing drops per application. Moreover the EDG increases the time needed for eye drop administration. The medications which are not a close fit with the EDG may increase the difficultly of instillation using the device. Older patients and those with more education are less likely to succeed with the EDG. The results also suggest that if participants received better instructions, the experienced glaucoma patients can improve eye drop instillation performance. Clinicians should regularly check to determine whether their patients need more advice regarding eye drop instillation.

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