Appropriateness and Determinants of Proper Administration Technique of Ocular Hypotensive Agents among Glaucoma Patients in Menelik II Referral Hospital, Ethiopia

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Abstract

Introduction: Appropriate administration of ocular hypotensive agents is required to lower an elevated intraocular pressure, prevent progressive damage of optic nerve head and visual field loss.

Objective: The main purpose of the study was to assess appropriateness of administration technique of ocular hypotensive agents and to identify factors associated with the proper technique.

Methods: A hospital-based cross-sectional study was conducted among 359 study participants in Menelik II Referral Hospital from June, 2015 to July 3, 2015. Eligible patients were interviewed and their medical charts were reviewed using a pretested structured questionnaire. Administration technique was assessed using nine-items of World Health Organization guide and associated factors were identified using multivariate binary logistic regression analysis. The association was declared significant at p<0.05.

Results: The rate of appropriate administration technique was 17.3%. Patients with advanced glaucoma (AOR=3.46, 95% CI: 1.09-10.97, p<0.035) and who had a more frequent follow-up (AOR=5.94, 95% CI: 1.19-29.62, p<0.030) were significantly associated with the appropriate administration technique. Patients with primary angle closure glaucoma (AOR=0.0, 95% CI: 0.00-0.25, p=0.022) and open angle glaucoma (AOR=0.0, 95% CI: 0.00-0.36, p=0.027), who immediately administered a second drop (AOR=0.0, 95% CI: 0.01-0.58, p=0.027), who experienced a side effect (AOR=0.13, 95% CI: 0.02-0.92, p=0.041) and who had low vision (AOR=0.0, 95% CI: 0.00-0.37, p<0.024) were inversely associated with the technique.

Conclusion: The administration technique was poor and sub-optimal according to the World Health Organization guide. Adoption and implementation of the guide are required to improve the instillation proficiency and optimize the glaucoma therapy.

Keywords: Administration technique; Ocular hypotensive agents; Glaucoma

Abbreviations
AOR: Adjusted Odds Ratio; CI: Confidence Interval; COR: Crude Odds Ratio; EDAT-9: Nine-Item Eye Drop Administration Technique; IOP: Intraocular Pressure; OHAs: Ocular Hypotensive Agents; SD: Standard Deviation; WHO: World Health Organization

Introduction
Glaucoma is a progressive optic neuropathy, often asymptomatic, caused by the death of the retinal ganglion cells and their fibers [1,2]. Worldwide, glaucoma is the leading cause of irreversible blindness. In 2013, the number of people (aged 40-80 years) with glaucoma worldwide was estimated to be 64.3 million and will be increased to 76.0 million by 2020 and 111.8 million by 2040, disproportionately affecting people residing in Africa and Asia [2].

The prevalence of glaucoma is high among Africans with an early onset and rapid progression of the disease [3]. Other studies also highlighted that glaucoma, predominantly open-angle glaucoma, is a public health problem in sub-Saharan Africa [4].

The medical management of glaucoma using ocular hypotensive agents (OHAs) is the first line option to lower the intraocular pressure (IOP); as level of the IOP is an important predictor of glaucoma prognosis [5,6]. Without appropriate administration technique of hypotensive eye drops, an elevated IOP may lead to progressive optic nerve damage and deterioration of the visual field and eventually to blindness [7,8].

The World Health Organization (WHO) recommended administration technique for eye drops includes application of the prescribed amount of eye drop into a pocket of the lower cul-de-sac that is created by pulling with washed index and thumb fingers, and
Study setting, period and design

A hospital-based cross-sectional study was conducted at the glaucoma clinic of Menelik II Referral Hospital, Addis Ababa, Ethiopia. Eligible patients, who attended the clinic during the course of the study (June, 2015 to July 3, 2015), were interviewed and their medical records were reviewed for the type and severity of glaucoma, intraocular pressure and visual acuity.

Inclusion and exclusion criteria

Patients who were 18 years old and above, with the diagnosis of glaucoma or ocular hypertension, were on OHA s for one or both eyes for at least 6 months, had regular follow-up and had not undergone either laser or glaucoma surgery in the previous 3 months were enrolled in the study.

Glaucoma patients with post-operative follow-up, on systemic glaucoma drugs only, on any anti-inflammatory or anti-infective eye drops only, which were not willing to give informed written consent and those enrolled in the pretest, were excluded from the study.

At the clinic, glaucoma diagnosis was made based on the presence of elevated IOP that is >20 mmHg, gonioscopy findings, characteristic optic nerve head damage (vertical disc excavation of >0.4, diffuse or focal thinning, or notching of the neuroretinal rim; or asymmetry of the vertical cup-disc ratio of 0.2 between eyes) and/or visual field defect. Glaucoma severity was diagnosed as early, moderate and advanced based on the Canadian glaucoma strategy [11].

Data collection and analysis

The data collection tool was formulated in English and then translated to Amharic, a national language, and then back again to English to maintain consistency of the meanings. The data were collected by three trained ophthalmic nurses, who had more than 3 years work experience at the clinic. To maximize the quality of the data, the data collection tool was pre-tested in 5% of the sample size (18 patients). Completeness of the data collected was supervised and monitored adequately by the first investigator every day.

The appropriateness of administration technique was assessed using nine-items of Eye Drop Administration Technique (EDAT-9) which is a WHO recommended procedure [9] in alignment with different studies [2,6,12]. The eye drop application procedure includes hand washing; not touching the dropper's opening tip against eye, face, hand or anything else; pulling down lower eyelid to form a pocket or “gutter” while slightly tilting head up; and applying the prescribed drop in the “gutter” correctly. After application, the eye should be closed for at least 2 minutes, and without massaging, blinking or squeezing the eyelids. Occulting the puncti, openings to the naso-lacrimal route, for 2 minutes immediately after instilling drops is also recommended.

In this study, patients were asked to demonstrate how they routinely applied their eye drops and then reaffirmed with nine questions. These questions comprised of three responses with value “0” representing “rarely/never”, “1” indicating “often” and “2” signifying “always/usually” except questions number two and seven in which case the values of “0” and “2” were reversed for “always/usually” and “rarely/never” respectively. The maximum score was eighteen and the individual patient’s score was made binary in to appropriate and inappropriate administration technique.

The filled-in forms were checked for completeness of the data and cleaned prior to data entry. Data was entered using Epi Info version 3.5.3. Data analysis was carried out using Statistical Package for Social Sciences (SPSS® Statistics) program version 21 (Chicago, IL, U.S.A.). Descriptive statistics such as frequency, percentage, mean and standard deviation was also employed to summarize the patient’s socio-demographic and clinical characteristics and medication related information.

Univariate binary logistic regression analysis was performed to relate each variable to administration technique. From the result of univariate analysis, variables with p<0.02 were selected for multivariate binary logistic regression analysis. This multivariate regression analysis was used to assess factors affecting administration technique of OHAs and to estimate the odds ratios (OR), 95% confidence intervals (CI) and p-values. The association was declared significant at p<0.05.

Operational definitions

Appropriate administration technique was operationally defined as the accomplishment of the critical instilling procedures and/or scored a comparative result, that is, more than twelve points from the total of eighteen score points. On the other hand, the inappropriate administration technique was defined when the patient did not accomplish at least one of the critical instilling procedures and/or did not score a comparative result, that is, when the participant scored less than or equal to twelve points from the eighteen score points.
Critical instilling procedures are procedures, if followed succinctly, can effectively increase the ocular bioavailability of OHAs, decrease the systemic adverse effects of OHAs and minimize microbial contaminations.

Results
The socio-demographics and clinical characteristics of the study participants are summarized in Table 1. Among 359 study participants, about half of the patients (n=18, 50.4%) were in the age group of 61-80 years (mean: 60.91; SD: ± 12.34 years; range: 18 to 88 years). Large numbers of the patients were males (n=247, 69.0%). Retired patients accounted for about one third (n=115, 32.0%) of the study participants. The majority of the patients (n=322, 89.7%) lives in urban. Concerning the educational level, lower education (elementary school and/or below) accounted for 63.9% (n=229) of the study participants (Table 1).

Table 1: Socio-demographic and clinical characteristics of patients attending the glaucoma clinic, Menelik II Referral Hospital.

| Variables                        | Frequency | Percent |
|----------------------------------|-----------|---------|
| **Age**                          |           |         |
| 18-40                            | 22        | 6.1     |
| 41-60                            | 149       | 41.5    |
| 61-80                            | 181       | 50.4    |
| ≥ 81                             | 7         | 1.9     |
| **Sex (n=358)**                  |           |         |
| Male                             | 247       | 69.0    |
| Female                           | 111       | 31.0    |
| **Educational level (n=358)**    |           |         |
| Illiterate or non-formal education | 109     | 30.4    |
| Elementary school (Grade 1 - 8)  | 120       | 33.5    |
| High school (Grade 9 - 12)       | 73        | 20.4    |
| Diploma and/or above             | 56        | 15.6    |
| **Place of residence (n=358)**   |           |         |
| Rural                            | 36        | 10.1    |
| Urban                            | 322       | 89.9    |
| **Occupation**                   |           |         |
| Retired                          | 115       | 32.0    |
| Employee (paid work)             | 79        | 22.0    |
| Self-employed (merchant)         | 34        | 9.5     |
| Other(s) (house wife, farmer student, unemployed, prisoner) | 131 | 36.5 |
| **Types of glaucoma (n=341)**    |           |         |
| Pseudoxfoliative glaucoma        | 138       | 40.5    |
| Primary open angle glaucoma      | 93        | 27.3    |
| Primary angle closure glaucoma   | 48        | 14.1    |
| Normal tension glaucoma          | 5         | 1.5     |
| Secondary glaucoma               | 3         | 0.9     |
| Other (s) (ocular hypertension, juvenile glaucoma) | 54 | 15.8 |

According to the medical records of the study participants, the most prevalent type of glaucoma was pseudoxfoliative glaucoma, accounted for 40.5% (n=138) followed by primary open angle glaucoma (n=93, 27.3%). The stage of glaucoma was recorded as advanced, moderate and early accounting for 24.1% (n=65), 64.1% (n=173) and 11.9% (n=11.9) of the patients respectively.

The mean duration of glaucoma diagnosis was 5.6 years (SD: ± 5.48 years; range: 6 months to 28 years) and the mean duration of applying OHAs was 5.35 years (SD: ± 5.30 years; range: 6 months to 28 years). The average frequency of follow-up per year was about three months (mean: 3.05 months; SD: ± 1.32 months).

Concerning medication related factors, three hundred fifty patients (97.5%) had been using one and/or two OHAs as depicted in Table 2. Combination of eye drops accounted for about half (n=185, 51.5%) of the prescribed medications followed by timolol as a monotherapy (n=158, 44.0%). In addition to this, about one in three of the patients (n=123, 32.8%) admitted that they waited more than five minutes to administer the second or consecutive drop. Above half (n=200, 56.0%)
of the patients reported that they did not experience an immediate side effect(s) of the OHAs (Table 2).

| Variables                              | Frequency | Percent |
|----------------------------------------|-----------|---------|
| Number of medications                  | One       | 174     | 48.7   |
|                                        | Two       | 176     | 48.8   |
|                                        | Three or more | 9     | 2.5    |
| Type of glaucoma medications           | Timolol   | 158     | 44.0   |
|                                        | Latanoprost | 1     | 0.3    |
|                                        | Pilocarpine | 2     | 0.6    |
|                                        | Other(s) (dorzolamide, dorzolamide+timolol, brimonidine, betaxolol) | 13 | 3.6 |
|                                        | Two or more combination of the eye drops | 185 | 51.5 |
| Time elapsed to administer the second or consecutive drop (n=183) | Immediately | 11 | 6.0 |
|                                        | 1-5 minutes | 49 | 26.8 |
|                                        | 5-10 minutes | 54 | 29.5 |
|                                        | >10 minutes | 69 | 37.7 |
| Immediate experience of side effect (n=357) | Yes | 157 | 44.0 |
|                                        | No         | 200     | 56.0   |

Table 2: Medication related factors for patients attending the glaucoma clinic, Menelik II Referral Hospital.

According to the medical charts of the study participants, the mean IOP, in mmHg, in the right eye and left eye was 17.8 (SD: ± 7.7; range: 8 to 52) and 18.3 (SD: ± 8.8; range: 6 to 61), respectively. Corresponding to the international council of ophthalmology's classification for visual acuity [13], about one-third of the patients had (near-) normal vision (n=122, 34.3%), low vision (n=130, 36.6%) and (near-) blindness (n=115, 32.3%).

Assessment of patients' response to the nine-item WHO recommended administration technique revealed that 17.3% (n=62) of the patients were appropriately administering the prescribed regimen of their OHAs (Table 3).

| Administration Technique of Ocular Hypotensive Agents | Response |
|-------------------------------------------------------|----------|
|                                                       | Frequency (%) |
|                                                       | Always/Usually | Often | Rarely/Never |
| Remembering to wash hands thoroughly with soap and water before the procedure | 144 (40.1) | 166 (46.2) | 49 (13.6) |
| Touching the dropper’s opening against eye, face, hand or anything else | 26 (7.2) | 143 (39.8) | 190 (52.9) |
| Pulling lower eyelid down to form a pocket or “gutter” while slightly tilting head up | 37 (10.3) | 98 (27.3) | 224 (62.4) |
| Positioning the tip of bottle so that it does not come closer than two centimeters above lower lid | 159 (44.3) | 112 (31.2) | 88 (24.5) |
| Applying the prescribed amount of doses in the “gutter” correctly | 199 (55.4) | 146 (40.7) | 14 (3.9) |
| Closing eyes for at least two minutes after instilling of the medication | 277 (77.2) | 49 (13.6) | 33 (9.2) |
| Shutting, massaging eye too tight and/or blinking or squeezing eyelids after applying the drops | 27 (7.5) | 107 (29.8) | 225 (62.7) |
| Occulting naso-tacrical route for at least two minutes immediately after instilling drops | 8 (2.2) | 5 (1.4) | 346 (96.4) |
Using a clean tissue, handkerchief or others to absorb excess eye drops that run onto the cheeks

| Cut off       | Frequency (%) |
|---------------|---------------|
| ≤ 12          | 297 (82.7)    |
| >12           | 62 (17.3)     |

Table 3: Summary of glaucoma patients’ response to the nine-item administration technique at the glaucoma clinic, Menelik II Referral Hospital.

The results of multivariate logistic regression analysis for factors associated with the appropriate administration technique were summarized in Table 4 after controlling the independent variables. Variables with p-value less than 0.2 from the univariate logistic regression analysis (including sex, marital status, religion, occupation, type of glaucoma, severity of glaucoma, follow-up schedule per year, previous management of glaucoma, number of medications, type of medications, time elapsed to administer the second or consecutive drop, side effects of medications and visual acuity) were incorporated in to multivariate logistic regression analysis. Accordingly, factors considered potentially to predict proper administration technique were the type of glaucoma, severity of glaucoma, follow-up schedule, time elapsed to administer the second or consecutive drop, immediate experience of side effects and visual acuity (Table 4).

| Variables                        | Administration Technique, n (%) | COR (95% CI) | AOR (95% CI) |
|----------------------------------|---------------------------------|--------------|--------------|
|                                  | Inappropriate | Appropriate  |              |              |
| Types of glaucoma                |                  |              |              |              |
| Pseudoexfoliative                | 111 (80.44)      | 27 (19.56)   | 1.00         | 1.00         |
| Secondary                        | 3 (100.00)       | 0 (0.00)     | 0.00 (0.00,-)| 9.9E+6 (0.00,-) |
| Primary angle closure            | 38 (79.17)       | 10 (20.83)   | 1.08 (0.48, 2.44) | 0.01 (0.00, 0.25)* |
| Normal tension                   | 3 (60.00)        | 2 (40.00)    | 2.74 (0.44, 17.20) | 16.73 (0.83, 3361.56) |
| Primary open angle               | 79 (85.00)       | 14 (15.00)   | 0.73 (0.36, 1.48) | 0.01 (0.00, 0.36)* |
| Other(s)                         | 49 (90.74)       | 5 (9.26)     | 0.42 (0.15, 1.15) | 0.00 (0.00,-) |
| Severity of glaucoma             |                  |              |              |              |
| Early                            | 27 (84.40)       | 5 (15.60)    | 0.92 (0.33, 2.59) | 3.65 (0.72, 18.57) |
| Moderate                         | 144 (83.24)      | 29 (16.76)   | 1.00         | 1.00         |
| Advanced                         | 49 (75.40)       | 16 (24.6)    | 1.62 (0.8, 3.24) | 3.46 (1.09, 10.97)* |
| Follow-up schedule per year      |                  |              |              |              |
| 1-2 times                        | 10 (83.33)       | 2 (16.67)    | 1.02 (0.2, 4.83) | 7.76 (0.27, 226.49) |
| 3-4 times                        | 188 (83.55)      | 37 (16.45)   | 1.00         | 1.00         |
| 5-6 times                        | 46 (78.00)       | 13 (22.00)   | 1.44 (0.7, 2.92) | 3.52 (0.95, 13.07) |
| >6 times                         | 53 (84.10)       | 10 (15.90)   | 0.96 (0.45, 2.05) | 5.94 (1.19, 29.62) * |
| Time elapsed to administer second or consecutive drop | | | | |
| Immediately                      | 10 (90.90)       | 1 (9.10)     | 0.25 (0.07, 0.94) | 0.01 (0.0, 0.58)* |
| 1-5 minutes                      | 42 (85.72)       | 7 (14.28)    | 0.72 (0.26, 1.96) | 0.11 (0.00, 3.57) |
| 5-10 minutes                     | 51 (94.45)       | 3 (5.55)     | 0.43         | 0.01 (0.00, 1784.61) |
to patients with moderate glaucoma. In contrast, the odds of administering an eye drop appropriately for patients with advanced glaucoma were almost threefold (AOR=3.46, 95% CI: 1.09 - 10.97, p< 0.035) more compared to patients with moderate glaucoma.

Another significant factor was the average frequency of follow-up per year. The odds of administering an eye drop appropriately for patients with more frequent follow-up (more than six times per year) were about six fold (AOR=5.94, 95% CI: 1.19-29.62, p< 0.030) more compared to patients whose follow-up were less frequent (three-four times) per year.

The odds of administering an eye drop appropriately for patients who immediately administered their second or consecutive dose were 99% (AOR=0.0, 95% CI: 0.00-0.36, p<0.027) less compared to individuals who waited more than ten minutes to administer the second or consecutive drop. The odds of administering an eye drop appropriately for patients who experienced an immediate side effect were also 87% (AOR=0.13, 95% CI: 0.02-0.92, p<0.041) less compared to individuals who did not experience the side effect. Likewise, the odds of administering an eye drop appropriately for patients who had low vision were 99% (AOR=0.0, 95% CI: 0.00 -0.37, p<0.024) less compared to patients who had (near-) normal vision.

Discussions

The study assessed administration technique of OHAs among glaucoma patients in Menelik II Referral Hospital, according to the WHO recommended procedures. Accordingly, the administration technique in the present study was improper for the majority of the study participants (82.7%) which was comparable to a study done in India with 90% rate [14]. The expected cause of this immense finding might be stemmed from inadequate provision of continuous education regarding eye drop administration technique from health care providers. This was substantiate das the majority of the study participants responded that they did not obtain adequate/relevant information about eye drop administration from their physicians or pharmacists and leaflets/brochures.

This finding was, however, higher compared to the findings of developed countries such as 44 % and 42.1% in the USA [15,16], 54.1% in the UK [17], 47% in Greece [7], and 33.8% in Canada [18]. This enormous dissimilarity might have emanated from differences in the assessment tool used; characteristics of study population and from the fact that developed countries have better health facilities.

This study identified potential predictors of administration technique. Severity of glaucoma was significantly associated with the appropriate instillation technique, that is, patients with advanced glaucoma were more likely to appropriately administer their medications compared to patients with moderate glaucoma. This might be attributable to the prudence of these patients due to fear of glaucoma progression and sight loss [19].

The odds of administering an eye drop appropriately for patients who had a more frequent follow-up were almost six fold more compared to patients with a less frequent follow-up. Patients with regular and close follow-up might have obtained repeated guidance and information from their care providers and might pay more attention to their disease and medications than patients with a lesser follow-up.

On the other hand, patients with primary angle closure and primary open angle glaucoma had lower odds of appropriate administration of eye drops as compared to patients with pseudoexfoliative glaucoma. This finding might be related to the aggressive nature of the pseudoexfoliative glaucoma that might lead to the necessity of more attention.

The other factor that was inversely associated with the proper administration technique was the time elapsed to administer the second or consecutive drop. The odds of administering eye drop appropriately for patients who had immediately administered the second or consecutive drop were 99% lower compared to patients who had waited more than ten minutes. Immediate administration of the second or consecutive dose might be a sign of hastiness or a condition effect.

Table 4: Multivariate logistic regression analysis of factors associated with the appropriate administration technique among patients attending the glaucoma clinic, Menelik II Referral Hospital.

| Side effects | Visual acuity | (Near-) normal | Low vision | (Near-) blindness |
|--------------|---------------|----------------|------------|------------------|
| Yes          | 130 (82.20)   | 27 (17.20)     | 0.01 (0.58, 1.77) | 0.13 (0.02, 0.92)* |
| No           | 166 (83.00)   | 34 (17.00)     | 1.00       | 1.00             |
| (Near-) normal | 95 (77.87)   | 27 (22.13)     | 1.00       | 1.00             |
| Low vision   | 103 (86.55)   | 16 (13.45)     | 0.55       | 0.01 (0.00, 0.37)* |
| (Near-) blindness | 98 (85.20) | 17 (14.80)     | 0.61       | 0.12 (0.0, 2.85)  |

AOR: Adjusted Odds Ratio; CI: Confidence Intervals; COR: Crude Odds Ratio.

*Statistically significant at p<0.05; p - values were calculated using multivariate logistic regression analysis.
of urgency and the patient, in turn, might able to miss the critical instilling procedures and hence affects the overall administration proficiency.

In addition to this, patients who experienced an immediate side effect were more likely to incorrectly administer their topical medications compared to those participants who did not experience the side effect. This is notable as experience of side effects could cause physical and/or emotional sensation and patients might prematurely discontinue the instillation procedures. Likewise, patients with low vision were less likely to properly administer their medications compared to patients with (near-) normal vision which was corresponded with previous studies [20,21]. Patients with low vision might not adequately administer their eye drops because of visualization problem in handling drug bottles and application of eye drops.

This study also identified that appropriate instillation proficiency was not significantly associated with age, educational level, intraocular pressure and the length of time the patients had been using eye drops, which was similar to previous studies [17,21]. The possible explanation for this finding might be the nature of study participants. The patients enrolled in this study were having a long duration of diagnosis and long experience of taking medications (with a mean of 5.60 years and 5.35, respectively) so that the patients' clinical related variables might have a lesser influence on the adequacy of administration technique.

The study had certain limitations. The cross-sectional nature of this study did not allow follow-up of the study participants and the results were relied on patients' response which could have provided a better design for identifying the factors associated with the administration technique.

**Conclusion**

The findings of this study have indicated that the appropriate administration technique of ocular hypotensive agents in Menelik II Referral Hospital was poor and suboptimal as to the WHO recommended administration technique, and having advanced glaucoma and frequent follow-up are the identified factors that were associated with the appropriate administration. Adoption and implementation of the technique are required to improve the instillation proficiency and optimize the glaucoma therapy.

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**Ethical Approval and Consent to Participate**

The study was undertaken after obtaining ethical clearance from the School of Pharmacy’s Ethical Review Committee, Research and Publication Committee of the Department of Ophthalmology, College of Health Sciences, Addis Ababa University and the Research Committee of Addis Ababa City Health Bureau. To ensure confidentiality, name and other identifiers were not recorded. Informed written consent was also obtained from the patients.

**Competing Interests**

The authors declare that they have no competing interests.

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**Authors’ Contributions**

TM designed, conducted the study and prepared the draft manuscript. WS and ATG supervised the study and reviewed the manuscript. All authors read and approved the final manuscript.

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