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ORIGINAL ARTICLE

Long-term benefit of reduced intraocular pressure in primary open-angle glaucoma patients in Ethiopia

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PURPOSE. *To determine the incidence of progression of primary open-angle glaucoma at individual levels of mean intraocular pressure (IOP) in patients in Ethiopia.* METHODS. *A retrospective, multicenter, cohort analysis of patient records with at least 5 years of potential follow-up were evaluated for risk factors associated with progressive optic disc and visual field loss.* RESULTS. *There were 300 patients with the potential of 5 years of follow-up. In total, 166 patients progressed before 5 years and 134 remained stable for the full 5-year follow-up period. Of the total sample, 84% of patients with IOPs ≤19 (n=117/139), 53% of patients with IOPs of 20 (n=9/17), 14% of patients with IOPs of 21–24 (n=9/63), and 0% of the patients with IOPs of ≥25 mmHg (n=0/79) remained stable over at least 5 years. The mean IOP was 17.4±2.1 in the stable group and 25.0±5.9 mmHg in the progressed group (p<0.0001). The highest average peak IOP was 24.5±4.5 in the stable group and 29.0±6.1 mmHg in the progressed group (p<0.0001). A multivariant regression analysis to determine risk factors for progression was positive for mean IOP (p=0.0097).* CONCLUSIONS. *This study suggests that IOP reduction in a developing country, despite potential limitations in diagnostic techniques, follow-up, and compliance, can be effective in reducing the risk of glaucomatous progression over long-term follow-up. (Eur J Ophthalmol 2010; 20: 00)*

KEY WORDS. *Africa, Ethiopia, Glaucoma, Intraocular pressure, Primary open-angle glaucoma, Target pressure*

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INTRODUCTION

Ethiopia is an Eastern African country that is an important commercial center with an approximate population of 74,777,981 (https://www.cia.gov/cia/publications/factbook/). Very little information is available regarding the types of glaucoma, treatment, or prognosis in Ethiopia.

Several previous studies have shown the prevalence of glaucoma generally in Ethiopia to be 8%ñ17% (1-3). However, Bedri and Alemu found that 25% of glaucoma patients had exfoliation (4). In addition, Teshome and Regassa showed the prevalence of exfoliation in cataract surgery patients was 39% (5).

More recently, Mulugeta and coworkers **[QUERY: Please add reference]** found in 415 glaucoma patients that the overall prevalence of exfoliation glaucoma was 17%. However, exfoliation glaucoma was most commonly found in one particular population, the Gurage tribe (33%). This study also found that patients were prescribed an average of 1.4±0.8 glaucoma medications, but 52% had admitted recent noncompliance. In contrast, 36% had undergone filtering surgery (internal data, PRN). Despite the above information on epidemiology, little information is available regarding the long-term results of open-angle glaucoma treatment in Ethiopia specifically or in developing countries generally.

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The purpose of this survey was to evaluate the long-term outcome of the treatment of primary open-angle glaucoma in and around Addis Ababa, Ethiopia.

METHODS

Patients

This study was a retrospective, non-interventional analysis from a prospectively gathered glaucoma patient cohort. Patients were chosen consecutively from the glaucoma clinic appointments of the one of the authors (A.M.A.) at the Ras Desta Hospital in Addis Ababa, Ethiopia. All examined patients who met entry criteria were included.

Each included patient had a diagnosis of primary open-angle glaucoma. These patients demonstrated deep anterior chambers without signs of secondary glaucomas (e.g., exfoliation material, pigment dispersion, neovascularization, or inflammatory products). On funduscopy, patients showed typical glaucomatous optic disc damage (i.e., neural rim thinning or notching, saucerization, thin nasal rim, or total cupping). Access to automated visual field testing and gonioscopy are limited in Ethiopia. Patients must have had at least 5 years (with at least 9 clinic visits) of follow-up available under the direction of the treating physician (A.M.A.). Patients also must have been untreated at their initial ophthalmic examination at the Ras Desta Hospital.

Excluded from this study were patients with congenital, juvenile, secondary, narrow angle, or normal-tension glaucoma (patients with a known history of an untreated intraocular pressure [IOP] never >21 mmHg). Also excluded from this study were patients thought to demonstrate progressive nonglaucomatous visual loss and those in whom the posterior pole could not be adequately visualized.

Procedures

Patients included in this study were consecutively considered as they were examined at the hospital eye clinic (inclusion visit). Following the examination, the included patientís records were reviewed to collect data for this study. Data collection began from the patientís first examination at the Ras Desta Hospital. This visit must have occurred at least 5 years prior to the inclusion visit (±1 year) in order to assure the potential of at least 5 years of follow-up data. The initial untreated IOP was excluded from analysis as it did not represent a level that would accurately reflect a patientís long-term treatment outcome.

Data were recorded from each available visit included in the follow-up period. Data were gathered regarding stable glaucoma for as long as 5 years. In contrast, data were collected from the records of progressed patients only until the time the glaucoma worsened. Data were not recorded after the time of any progression so the information included in this study could reflect the ocular status leading up to the worsening of the glaucoma.

Data collection recorded from available visits included date of examination, Goldmann applanation tonometry, Snellen visual acuity, and dilated ophthalmoscopy when performed. Routine follow-up visits typically were performed every 3ñ6 months. Dilated optic disc examinations generally were completed yearly or more frequently if required. At dilated examinations, the optic disc was examined by stereoscopic techniques (90 Volk lens). The principal investigator (A.M.A.) evaluated each patient during the follow-up period.

The principal investigator alone determined progression. In each case, progression must have been noted in the chart or at the inclusion visit. Generally, criteria for progression were an increase in thinning of the neural rim or worsened visual acuity not associated with other causes. Patients without progression noted were assumed to be stable. If the patient record seemed inconsistent with either progression or stable, clinical findings were reviewed with the treating physician to assure accuracy.

Statistics

Data collection and statistical analysis between patients who were either stable or progressed were performed as follows. All data were 2-sided and unpaired. A value of 0.05 was selected to determinate statistical significance. A Student t test was used to analyze data between progressed and non-progressed groups for patient age, and the mean as well as peak IOPs during the follow-up period.

An F test analyzed the differences between the variance of each individual patientís IOPs measured during the follow-up period. A chi-square test was used to analyze differences between groups of non-ordered scores such as left or right eye, gender, ethnicity, and religious preference. When possible, a Fisher exact test was used to analyze differences of non-ordered scores which had at least one value of <5 in a 2 x 2 table. A Mann-Whitney U-test was used to determine statistical differences between groups in ordered scores that included cup-to-disc ratio, visual acuity,

and number of glaucoma medicines. A multivariant analysis was performed to search for risk factors associated with progression. If both eyes of a patient met the criteria for entrance into the study, only one eye was randomly chosen to be analyzed.

RESULTS

Patient characteristics

This study included 300 patients (300 eyes) with primary open angle glaucoma. Table I describes the patient characteristics at baseline (visit 1) between the progressed and non-progressed groups at baseline. Statistical differences at baseline between groups existed for age, gender, ethnic origin, optic disc ratio, IOP, and visual acuity ($p \leq 0.0028$).

Patient follow-up characteristics

The follow-up data are shown in Table II. During the follow-up period, patients who progressed demonstrated a higher mean IOP (25.0±5.9) than did the non-progressed patients (17.4±2.1 mmHg, $p<0.0001$). However, the initial reduction in pressure between visits 1 and 2, when the patient presumably received initial treatment, was more for progressed (10.7±6.0 mmHg) than non-progressed patients (8.4±4.5 mmHg, $p=0.0004$).

Of the total sample, 84% of patients with pressures ≤19 (n=117/139), 53% with a pressures of 20 (n=9/17), 14% with pressures with 21–24 (n=9/63), and 0% of with pressures of ≤25 mmHg (n=0/79) remained stable over at least 5 years. Figure 1 demonstrates the incidence of progression at various mean pressure levels. Generally, across all patients, pressures of ≤19 mmHg provided the greatest likelihood of preventing progression over 5 years.

In addition, progressed patients were prescribed more glaucoma medications at the end of the follow-up period ($p<0.0001$), but had fewer trabeculectomies ($p<0.0001$). Also, progressed patients demonstrated a shorter follow-up time and a fewer number of visits ($p<0.001$) as would be expected from the study design. In addition, the peak IOP and the standard deviation of the pressure were higher in the progressed group ($p<0.0001$ and $p<0.01$, respectively).

TABLE I - BASELINE PATIENT CHARACTERISTICS (MEAN ± STANDARD DEVIATION)

	Progressed (n = 166)	**Stable (n = 134)**	**p value**
Age, y	65 ± 10.8	62 ± 9.8	0.0028
Gender			
Female	47	52	<0.0001
Male	119	82	
Tribe			
Amhara/Tigre	73	75	0.0001
Oromo	45	23	
Gurage	38	28	
Other	10	8	
Religion			
Christian	139	119	0.28
Muslim	26	15	
Not specified	0	1	
Study eye			
Right	79	70	0.33
Left	87	64	
Cup-disc ratio (study eye)	0.8 ± 0.1	0.6 ± 0.1	<0.0001
Visual acuity (study eye)	5.5 ± 1.9	3.4 ± 1.5	<0.0001
Intraocular pressure (mmHg) (study eye)	36.9 ± 8.2	30.8 ± 6.3	<0.0001
No. of medications (both eyes)	0	0	

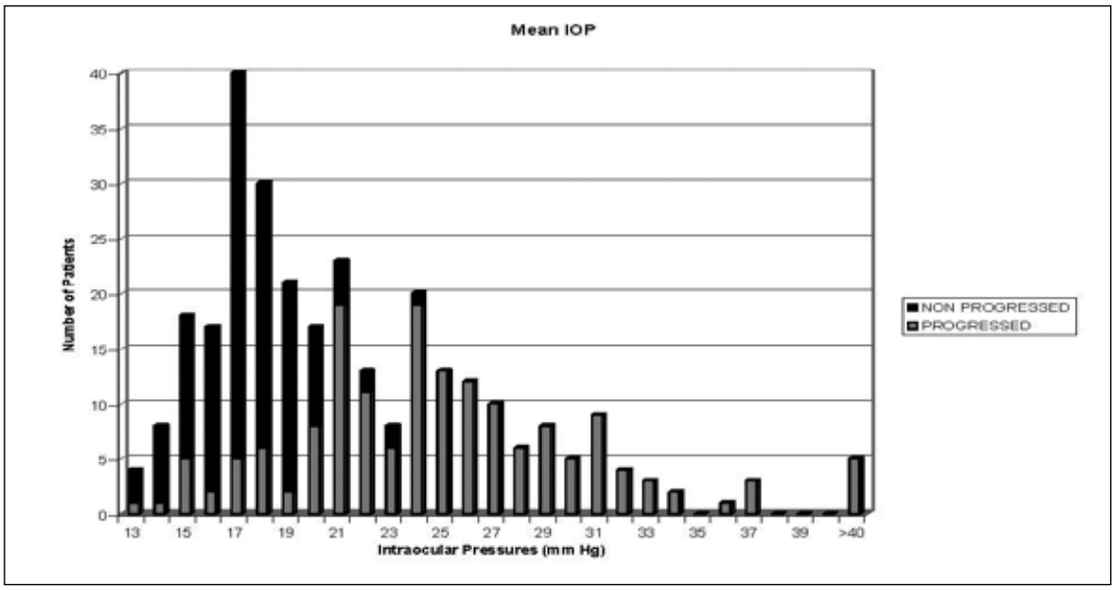

Fig. 1 - *Incidence of progression at various mean pressure levels with black signifying non-progressed and gray progressed.*

TABLE II - PATIENT CHARACTERISTICS (MEAN ± STANDARD DEVIATION) DURING STUDY

	Progressed (n = 166)	**Stable (n = 134)**	**p value**
Peak intraocular pressure, mmHg	29.4 ± 6.1	24.5 ± 4.5	<0.0001
Mean intraocular pressure, mmHg	25.0 ± 5.9	17.4 ± 2.0	<0.0001
Variance of intraocular pressure	34.5	4.0	<0.01
No. of visits	6.0 ± 1.7	9.9 ± 0.1	<0.001
Length of follow-up (progressed, y)	2.4 ± 1.1	5.4 ± 0.6	<0.001
No. of trabeculectomies	0.3 ± 0.4	0.6 ± 0.5	<0.0001
Total medications	1.7 ± 0.6	1.2 ± 0.5	<0.0001

TABLE III - RESULTS OF THE MULTIVARIANT REGRESSION ANALYSIS FOR RISK FOR PROGRESSION OVER 5 YEARS

	p value
Age	0.91
Mean intraocular pressure	0.0097
Peak intraocular pressure	0.32
Gender	0.16
Coefficient of variation normal	0.65
Coefficient of variation mild	0.39

R^2 = 0.048.

Risk factors for progression

Multivariant regression analysis results are shown in Table III. This analysis showed that the mean IOP was a risk factor for progression (p=0.0097).

DISCUSSION

Controversy still exists over the proper treatment endpoints for patients with glaucoma. Several historical and recent studies have demonstrated not only the benefit of IOP reduction in primary open-angle glaucoma, but have

indicated specific target pressures that help prevent progressive glaucomatous damage. These reports have shown that IOPs of between 13ñ18 mmHg over 5 years helped prevent glaucomatous progression with approximately 5%ñ15% of patients with primary open-angle and 28% with exfoliation glaucoma worsening over 5 years (1, 2, 6-11). Several studies, however, have indicated a further benefit in advanced glaucoma patients of pressures as low as 12ñ13 mmHg (12, 13).

In contrast, generally IOPs above 18 mmHg have led to greater incidences of progressive glaucomatous damage. For example, in several reports patients with slightly higher mean pressures (19-21) progressed in approximately 50%–67% of cases, and progression occurred with pressures ≥22 mmHg in almost 100% of patients (3, 6). However, the level of mean or peak pressures that would provide safety for all patients with primary open-angle glaucoma has not yet been defined clearly. In a separate way of evaluating the effect of the pressure, the Early Manifest Glaucoma Trial showed that for every 1 mmHg alteration in pressure there was a corresponding proportional change of 11% in the glaucomatous progression rate (14).

The purpose of this survey was to evaluate the long-term outcome of the treatment of primary open-angle glaucoma in and around Addis Ababa, Ethiopia.

This study found that glaucoma patients in Ethiopia who progressed within 5 years had a mean IOP of 25 mmHg while those who did not progress demonstrated a mean pressure of 17 mmHg. Multivariant regression analyses helped confirm that mean IOP was a risk factor for progression over 5 years. Further, the peak IOP and standard deviation of the pressure were also statistically higher in the progressed group. In addition, although the initial reduction of therapy between visits 1 and 2 was more with progressed than non-progressed patients, this greater decrease was insufficient to control the pressure to the level of the progressed group. This finding, along with the higher initial pressures in the progressed group, may explain, at least in part, their need for additional medical therapy to control their pressure as well as their higher tendency towards progression itself. The absolute IOP level which best characterized the break between relative safety from progression to that level which was associated with progression was ≤19 mmHg. Patients with this level of pressure or below over 5 years remained stable in 84% of cases. Further, little difference existed in progression rates for those with pressures between 13 and 19 mmHg. In contrast, patients with a mean pressure of 20 mmHg progressed in 53% of instances. However, patients with 21–24 mmHg remained stable at similar rates at each individual pressure level in 14% of cases. Importantly, no patient with ≥25 mmHg failed to progress within 5 years.

The findings of this study are consistent with past studies, noted above, which generally found that primary open-angle and exfoliation glaucoma patients in the United States and Europe remained stable in 85 to 95% of cases with pressures of 18 mmHg or less (15-20). In addition, several but not all of these studies noted that the peak pressure and standard deviation of the pressure was also higher in progressed patients (16, 17).

This current analysis, however, is additive to the literature because it evaluated an African population in a developing country and the pressure requirements to maintain stability over 5 years. This is an important question for several reasons. First, because problems in Africa make consistent follow-up difficult, identifying a higher ìsafeî pressure than required in developed countries would reduce the cost and the demands for glaucoma treatment. However, in this current study similar target pressures were found in Ethiopia as in Europe and the United States. Second, several previous authors have suggested that patients of African heritage more easily progress to blindness (21). Consequently, people of black African heritage theoretically might require a lower target pressure than Caucasians. However, in this Ethiopian population the target pressure was similar to those described the United States in several studies by Stewart and coworkers (15-18). Further, in the work of Stewart and associates and several NIH-sponsored trials, African American race was not a risk factor for progression (12, 15-19).

Baseline characteristics were not generally the same between progressed and non-progressed patients. Progressed patients demonstrated older age, larger cup/disc ratio, worse visual acuity, and a higher pressure than non-progressed patients. These differences imply that treated patients who progressed ultimately were more advanced in their disease when they first presented to clinic. These findings speak to the need for early diagnosis in the setting of the developing world to help assure successful treatment long term.

Other baseline differences associated with progression were more demographic in nature and included male gender and Amhara/Tigre ethnicity. The reason why these characteristics were associated with progression was not clear by our results. The findings may imply cultural dif-

ferences within these groups that might lead to a delayed ocular examination or treatment noncompliance.

This study suggests that IOP reduction in a developing country, despite potential limitations in diagnostic techniques, follow-up, and compliance, can be effective in reducing the risk of glaucomatous progression over long-term follow-up.

This study was limited because visual field and advanced optic disc analyses by optical coherence tomography, confocal laser ophthalmoscopy (Heidelberg Retinal Tomography), or scanning laser polarimetry (GDx) are not available in Ethiopia. Consequently, progression was rated typically only by the optic disc examination. Further, access to medicines is more limited, especially to the prostaglandin analogs, and laser treatments are not available. In addition, this study was primarily retrospective in design. Further prospective studies are needed to confirm or challenge our results. In addition, more work is needed in developing countries generally in improving screening, diagnostic, follow-up, and treatment techniques.

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