



Improving the diagnostic accuracy of the nerve-fiber analyzer

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CCT-IOP correlation among Filipinos

0.4 mg/ml vs. 0.2 mg/ml Mitomycin-C in trabeculectomy

Treatment of ocular toxoplasmosis in pregnancy

The first reported case of Bardet-Biedl syndrome at UP-PGH

Landmark glaucoma trials: what they mean in clinical practice

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ANNOUNCEMENTS

PAO 2004 annual confab slated November 18-20

The Philippine Academy of Ophthalmology (PAO) will hold its 2004 annual convention on November 18 to 20 at the Shangri-La Hotel in Mandaluyong.

With the theme "Look the Future in the Eye," the convention focuses on pediatric ophthalmology and strabismus to draw attention to the growing number of blind and visually impaired children in the country.

"They are our hope and future," says PAO President Dr. Marcelino D. Banzon, citing the appropriateness of the theme. Yet, they are also the "most vulnerable" to the many causes of blindness and visual impairment, which are easily preventable with early screening and management, he adds.

Prominent international pediatric ophthalmologists and strabismologists have been invited to shed light on the different ophthalmic disease entities affecting children. Among them are Dr. Kenneth Wright, Dr. Mohamad S. Jaffar, Dr. Ken K. Nischal, Dr. John W. Shore, and Dr. Sonal Farzavandi. Meanwhile, Dr. Tekeyuki Akahoshi and Dr. Abhay Vasavada will share more pearls on phacoemulsification. The opening session will have as speaker civil society leader Victoria Garchitorea, president of Ayala Foundation.

Dr. Ma. Dominga B. Padilla, who heads this year's organizing committee, said PAO's 2004 meeting will have many "firsts." It will feature two new courses on topics that are becoming more and more important to ophthalmologists—ophthalmic photography and computerization of the ophthalmic practice. The annual photography contest will also include a category on digital photography. Also, all registered participants will get CDs containing a compilation of selected lectures.

Those wishing to participate may register at the PAO office at:

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Abstracts of presentations will be accepted until September 11. The original and two clear photocopies may be sent to the PAO Secretariat. Those who wish to submit their abstracts on-line may visit the PAO web site at www.pao.org.ph. Click on the link to the "2004 Annual Meeting."

Joint meeting with AAO eyed for 2005

To mark 60 years of organized ophthalmology in the country

The Philippine Academy of Ophthalmology will mark the 60th year of organized ophthalmology in the Philippines with a proposed joint meeting with the American Academy of Ophthalmology.

Dr. Romulo N. Aguilar, former PAO president and head of the committee undertaking preparations for the celebrations, said the proposal has been accepted by the AAO and a memorandum of understanding is due to be signed soon.

Dr. Aguilar said this marks the first time that the AAO is holding a joint meeting with a national ophthalmology organization, having done so in the past only with supranational organizations.

The meeting is slated November 28 to December 1 at

the Shangri-La Hotel in Mandaluyong.

The convention is also expected to draw participants from the Asia-Pacific region.

It will serve as a fitting highlight of the PAO's celebration of 60 years of organized ophthalmology in the country. Organized ophthalmology began in the Philippines in 1945 with the founding of the Philippine Ophthalmological and Otolaryngological Society.

Dr. Aguilar is joined in the anniversary celebration committee by Drs. Salvador Salceda, Alejandro de Leon, Marcelino Banzon, Ma. Dominga Padilla, Carlos Naval, Winston Villar, Teresita Castillo, Reynaldo Santos, Heriberto Guballa, Mary Rose Pe-Yan, and Ronald Yutangco.



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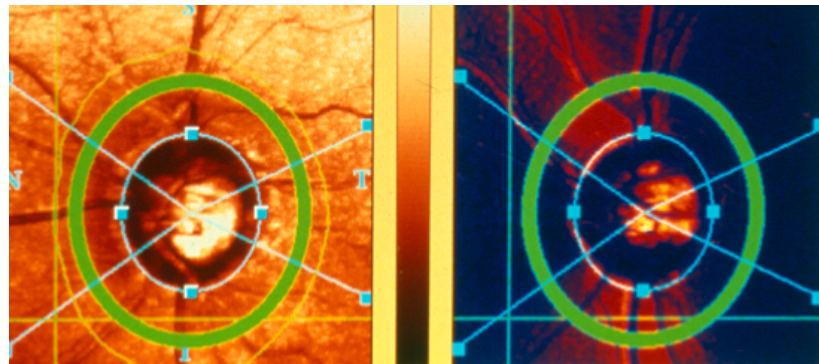
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Four major glaucoma trials have confirmed the beneficial effects of lowering intraocular pressure in open-angle glaucoma. But they also show that management of glaucoma patients must be individualized.

EDITORIAL

What is the gold standard in glaucoma diagnosis?

The ideal gold standard should be the best available method of differentiating between those with and without the disease.

Currently, the diagnosis of glaucoma is based on definitive changes in the optic-nerve head (ONH) and/or repeatable changes in the visual field tested by standard achromatic perimetry (SAP). Elevated intraocular pressure (IOP) defined as IOP greater than 21mm Hg was part of the definition of glaucoma more than 10 years ago. But several studies have shown that many patients with ocular hypertension demonstrated no signs of glaucomatous damage during follow-up periods of up to 20 years, even if the condition was left untreated.¹⁻⁴ Given the complex relationship between IOP and glaucoma damage, researchers and professional organizations emphasized a new glaucoma concept in which the disease was described as an optic neuropathy, with IOP as only one of several risk factors.⁵⁻⁷

In a single glaucoma examination, critical ONH evaluation is more sensitive and specific for diagnosing glaucoma than IOP measurement or visual field assessment. ONH evaluation has approximately 85% sensitivity and 90% specificity while visual-field examination has approximately 75% sensitivity and 95% specificity.⁸ Examination of either one alone, however, is inadequate because the correlation between structural and functional damage in glaucoma is not exactly linear, especially in the early stage of the disease. Several studies have shown that detectable damage to the ONH and retinal-nerve-fiber layer (RNFL) is generally present before detectable alteration in the visual field.^{9,10} Approximately 40 to 50% loss of ganglion cells was present before the first defect was detected in the visual field.¹¹

In recent years, several instruments have been developed to assist clinicians in detecting the presence or absence of glaucoma. They were tested for their accuracy against a "gold standard." In glaucoma, the choice of a gold standard poses several problems. Each of the tools employed in making the diagnosis of glaucoma involves looking at different aspects of the disease. In evaluating the ONH, one looks for the presence of structural damage. In visual-field testing, one looks at the functional damage. Generally, structural damage in the ONH corresponds to functional damage in the visual field with characteristic glaucomatous defects. In the early stage of the disease, however, there may already be structural damage in the ONH without detectable damage in the visual field (preperimetric stage). Hence, combining both features will increase the sensitivity and specificity in the assessment of glaucoma by standard methods.

Varying sensitivities and specificities have been reported for these new glaucoma instruments, the cause of which is probably an imperfect gold standard. The ideal gold standard should be the best available method of differentiating between those with and without the disease. It should effectively discriminate these groups across the full spectrum of the disease. Many times a "perfect" gold standard is still not available. As a result, an imperfect but considered the best available standard may be chosen as the standard of validity.

Many investigators used the glaucoma experts' diagnosis as the gold standard, which was derived from integrating the results of the different glaucoma tests (battery of glaucoma tests) as shown in the article on the *Diagnostic Properties of a Nerve-Fiber Analyzer* (see pages 66 to 72). Others used the definitive diagnosis of glaucoma derived after several years of following up the patient (natural history of the disease). The latter may be more accurate but more time consuming and difficult because of the long latency of the disease.

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Among the recently published randomized controlled trials in glaucoma, most investigators used the findings on SAP as definite diagnosis that glaucoma is present. This may be appropriate for the Advanced Glaucoma Intervention Study (AGIS)^{12, 13} or the Collaborative Initial Glaucoma Treatment Study (CIGTS)¹⁴ but for studies involving early glaucoma such as The Early Manifest Glaucoma Trial (EMGT)¹⁵ or the Ocular Hypertension Treatment Study (OHTS),⁴ a combination of glaucomatous optic-disc findings and/or visual-field defects is used.

Since the publication of the results of several landmark studies in glaucoma, much has been discussed about the role of IOP lowering. We have included in this issue a commentary on several of these randomized controlled studies, summarizing the results, outlining their strengths and weaknesses, and more importantly, analyzing their implications on and application to clinical practice.

—The Editor in Chief

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ORIGINAL ARTICLE

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The diagnostic properties of a nerve-fiber analyzer in glaucoma

Potential use as a screening
or diagnostic tool

ABSTRACT

Objective

To determine the diagnostic properties of the GDx 400 (Laser Diagnostic Technologies, San Diego, CA, USA) nerve-fiber analyzer in normal and in glaucoma patients compared with a battery of glaucoma tests used by glaucoma experts as gold standard.

Methods

Patients with and without glaucoma underwent a complete eye evaluation, automated perimetry, scanning laser polarimetry with the GDx 400, and optic-disc photography. Two glaucoma experts graded each study eye. Two-by-two tables were constructed for 5 GDx parameters (average thickness, superior average, inferior average, ellipse average, and ellipse modulation) and the GDx number. Receiver operating characteristic (ROC) curves were generated.

Results

The study included 355 patients (171 normal, 184 glaucoma). The mean values of the 5 GDx parameters were lower for the glaucoma than for the normal group. The sensitivity and specificity of the GDx 400 were 45.4% and 91.9% if the cutoff level of the GDx number was 71. Ellipse modulation (EM) measures have the best ROC curve with area under the curve of 0.725.

Conclusion

The GDx 400 nerve-fiber analyzer is primarily used as a screening tool to detect the presence or absence of glaucoma. Its accuracy can be improved with use of continuous corneal compensator.

Key words: *Glaucoma, Retinal nerve-fiber layer, Nerve-fiber analyzer, Scanning laser polarimetry*

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SCANNING laser polarimetry (SLP), exemplified by the GDx 400 nerve-fiber analyzer, allows noninvasive quantitative assessment of the retinal nerve-fiber layer (RNFL). Several studies¹⁻⁵ showed considerable overlaps in measurements among those suspected with glaucoma and those with early glaucoma. Sensitivities vary from 57% to 82% and specificities from 62% to 92%.⁶⁻⁷ These differences occurred depending on the cutoff for "abnormal" used. Other studies^{1,7} used logistic regression analysis and discriminant function and identified several GDx parameters that best differentiate normal from glaucomatous eyes.

In this study, the diagnostic properties (sensitivity, specificity, predictive value, likelihood ratio) of the GDx 400 in normal and in glaucoma patients were compared with a battery of glaucoma tests employed by glaucoma experts as gold standard. The receiver operating characteristic (ROC) curve was used to illustrate the relationship between sensitivities and specificities of five GDx parameters and the GDx machine.

METHODOLOGY

Patients were recruited from the Eye Referral Center (ERC) and the Glaucoma Section of the Department of Ophthalmology, Philippine General Hospital (PGH) between July 2000 and July 2002. Included in the study were patients between 30 and 79 years of age with visual acuity of at least 20/40 (6/12) with best correction. Those with significant media opacities that could preclude good scanning images, presence of retinopathy, or high refractive error of greater than -6 diopters were excluded. Only one eye per patient was included in the study.

The study complied with the Declaration of Helsinki and was approved by the Ethics Committees of the PGH and the Eye Referral Center. All subjects gave informed consent.

Each patient underwent the following examinations: complete eye evaluation, automated threshold perimetry 30-2 (Octopus 101, Bern, Switzerland or Humphrey Field Analyzer I 630, San Leandro, CA, USA), scanning laser polarimetry (GDx 400), optic disc photography (Canon 60UVI fundus camera, Tokyo, Japan).

Two glaucoma experts, masked from the GDx results, graded all the eyes included in the study. Eyes were classified as either normal or with glaucoma. The following aided the experts in making the classification:

1. An eye was considered normal if the visual field did not show any characteristic glaucomatous defects on standard achromatic perimetry (SAP), had an intraocular pressure (IOP) of less than 30 mmHg, had a cup-to-disc (CD) ratio of less than or equal to 0.5, and no suspicious glaucomatous damage on the optic-nerve head (ONH).
2. An eye was considered to have glaucoma if any one

of the following was present: cupping to the disc margin with associated enlargement of the peripapillary atrophy with or without detectable abnormalities in the visual field on SAP; glaucomatous abnormalities in the ONH such as disc hemorrhage; and abnormalities in the visual field characteristic of glaucoma damage.

During the grading sessions, information relating to each study eye was made available (visual-field printouts, IOP, ocular history and medications but no GDx results). All the available optic-disc photos were projected onto a screen at the same magnification for adequate comparison. The classification was done openly with discussions between the two graders. A consensus was arrived at for the diagnosis of each eye. If the disc cupping was more than 0.5, centrally located, with an intact neuroretinal rim, and no observable visual-field defect on SAP, it was classified as normal.

Data collected were entered into MS Excel (Microsoft Corporation, Redmond, WA, USA) worksheet and subjected to ROC curve analyses using Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS, Inc., Chicago, IL, USA). Two-by-two tables were constructed for five select GDx parameters, which included average thickness (AVE), superior average (SA), inferior average (IA), ellipse average (EA), and ellipse modulation (EM). Their sensitivities, specificities, predictive values, and likelihood ratios were obtained at varying cutoff levels for the presence or absence of glaucoma using Epi Info version 6 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

The GDx number (#)⁸ represented the overall probability of an eye having glaucoma. It was generated by the machine and derived by integrating all the GDx parameters and characteristics by means of neural network and comparing to an inherent database. Values ranged from 0 to 100; the higher the number, the higher the probability. Values 0 to 30 were considered normal; 31 to 70 glaucoma suspects; and 71 to 100 with glaucoma. Several two-by-two tables were generated at different cutoff levels for the presence or absence of glaucoma. A ROC curve was constructed to determine the best cutoff level.

RESULTS

Demographic characteristics

A total of 355 patients (144 males, 211 females) were included in the study. Mean age was 58 years. Mean visual acuity was 20/25 (6/7.5) (0.9). Mean IOP was 14.5 mm Hg (Table 1).

Patients in the glaucoma group were older ($p = 0.001$), had lower visual acuity ($p = 0.003$), had abnormalities in the visual field with lower mean sensitivity ($p < 0.001$), higher mean defect ($p < 0.001$), and larger loss variance or pattern

Table 1. Demographic and visual characteristics of patients.

	Without Glaucoma (n = 171)	With Glaucoma (n = 184)
Age (years)		
Mean	55	60
SD	11.0	10.7
Range	30 to 78	37 to 78
Male:female ratio	66:105	78:106
Visual Acuity		
Mean	0.92	0.84
SD	0.21	0.26
Range	0.00 to 1.33	0.00 to 1.33
Refraction (spherical equivalent)		
Mean	0.15	0.17
SD	1.72	1.74
Range	-6.12 to +3.75	-5.50 to +3.25
IOP (mm Hg)		
Mean	13.4	15.5
SD	3.5	5.6
Range	6 to 29	6 to 34
Visual Field Mean Sensitivity (decibels)		
Mean	22.72	16.93
SD	4.85	8.46
Range	2.20 to 30.1	1.9 to 29.1
Visual Field Mean Defect (decibels)		
Mean	4.6	8.98
SD	4.67	8.17
Range	-1.80 to 25.4	-2.20 to 25.4
Loss Variance (decibels)		
Mean	17.03	25.91
SD	18.56	24.38
Range	0.80 to 86.1	0.40 - 113.2
Vertical Cupping		
Mean	0.55	0.70
SD	0.14	0.20
Range	0.2 to 0.6	0.2 to 1.0
Horizontal Cupping		
Mean	0.53	0.68
SD	0.14	0.20
Range	0.20 to 0.5	0.25 to 0.9

standard deviation ($p < 0.001$). Many of those with glaucoma were on medication or had glaucoma surgery.

GDx parameters: mean values

The five GDx parameters (Table 2) showed lower mean values in the glaucoma group compared with the normal group ($p < 0.001$).

Validity analysis

Two-by-two tables were constructed for each GDx parameters and ROC curves were generated to determine the best cutoff level for the presence or absence of glaucoma.

Table 2. Values of the 5 GDx parameters.

GDx Parameters	Without Glaucoma (n = 171)	With Glaucoma (n = 184)	t-test p-value
AVE			
Mean	64.62	60.57	< 0.001
SD	12.70	11.15	
Range	44.25 to 120.75	38.25 to 94.0	
SA			
Mean	82.33	72.25	< 0.001
SD	18.83	15.85	
Range	46.25 to 134.5	41.50 to 126.25	
IA			
Mean	90.20	79.02	< 0.001
SD	19.19	18.88	
Range	54.50 - 149.50	40.50 to 142.50	
EA			
Mean	67.52	62.21	< 0.001
SD	12.66	11.51	
Range	43.75 - 104.0	37.75 to 98.0	
EM			
Mean	2.35	1.81	< 0.001
SD	0.61	0.77	
Range	0.69 to 4.36	0.58 to 3.98	

The sensitivities of the five GDx parameters ranged from 62% to 75%, and specificities from 46.8% to 65% (Table 3). The corresponding ROC curves did not show a rapid rise to the upper left corner; instead the curves were closer to the center diagonal line running from lower left to upper right. The positive predictive values ranged from 58.6% to 63.7% and the negative predictive values ranged from 57.1% to 63.6% (Table 3). At best, the GDx parameters were able to predict 60% of those with either a positive or a negative test.

Diagnostic properties of the GDx

The GDx number was the diagnosis generated by the GDx system and this was compared with the diagnosis given by the glaucoma experts. Different two-by-two tables were generated using several cutoff levels (Table 4).

The manufacturer's recommended cutoff level for glaucoma was GDx number 71. The sensitivity obtained on this level was 45.4% with a specificity of 91.9%. High false-negative errors were present. Lowering the cutoff level to 50 would improve the sensitivity to 67.4% and lower the false-negative errors but would also decrease the specificity to 77.8%. Looking at the ROC curve of the GDx (Figure 1), the point nearest the upper left corner has a sensitivity of approximately 68.7% and a specificity of 70%. This was obtained at a cutoff level of 44. The GDx number, which integrates all the GDx parameters, had the best ROC curve when compared with each of the five GDx parameters studied with an area under the curve of 0.732 (Table 5). The positive predictive value of the GDx number was much

Table 3. Sensitivities and specificities of the 5 GDx parameters using best cutoff level for the presence or absence of glaucoma.

Calculations from 2 x 2 tables	GDx Parameters (Best Cutoff Level)				
	AVE (65)	SA (77)	IA (87)	EA (67)	EM (2.11)
Sensitivity (%) (95% CI)	70.1 (62.9, 76.5)	72.7 (63.5, 77.7)	75.0 (69.4, 84.7)	68.5 (60.1, 75.8)	62.0 (56.9, 69.6)
Specificity (%) (95% CI)	46.8 (39.2, 54.5)	53.0 (48.2, 58.8)	54.0 (49.2, 58.5)	50.0 (43.2, 58.5)	65.0 (57.9, 72.0)
Predictive value positive (%) (95%CI)	58.6 (51.8, 65.2)	62.0 (54.5, 68.9)	63.7 (56.6, 70.3)	61.1 (53.9, 67.9)	59.9 (52.5, 66.9)
Predictive value negative (%) (95%CI)	59.3 (50.5, 67.5)	59.1 (51.3, 66.4)	63.6 (55.5, 71.1)	59.9 (51.7, 67.5)	57.1 (49.3, 64.7)
Likelihood ratio positive (95% CI)	1.50 (1.25, 1.82)	1.51 (1.23, 1.88)	1.63 (1.34, 2.0)	1.46 (1.21, 1.79)	1.39 (1.13, 1.71)
Likelihood ratio negative (95% CI)	0.56 (0.43, 0.73)	0.64 (0.51, 0.80)	0.53 (0.41, 0.68)	0.62 (0.49, 0.79)	0.70 (0.56, 0.87)

Table 4. Sensitivities and specificities of the GDx 400 using different cutoff levels of the GDx number for the presence or absence of glaucoma.

Calculations from 2 x 2 tables	Cutoff Level of GDx Number				
	< 71	< 65	< 60	< 55	< 50
Sensitivity (%) (95% CI)	45.4 (38.0, 52.9)	50.5 (43.1, 57.9)	58.5 (51.0, 65.6)	60.9 (53.4, 67.9)	67.4 (60.0, 74.0)
Specificity (%) (95% CI)	91.9 (86.5, 95.3)	90.1 (84.3, 93.9)	87.8 (81.7, 92.1)	83.0 (76.4, 88.2)	77.8 (70.7, 83.6)
Predictive value positive (%) (95% CI)	85.6 (76.6, 91.6)	84.5 (76.1, 90.5)	83.6 (75.8, 89.3)	79.4 (71.6, 85.6)	76.5 (69.1, 82.7)
Predictive value negative (%) (95% CI)	61.2 (55.0, 67.2)	62.9 (56.4, 68.9)	66.5 (59.9, 72.5)	66.4 (59.5, 72.6)	68.9 (61.8, 75.3)
Likelihood ratio positive (95% CI)	6.01 (3.54, 10.37)	5.08 (3.21, 8.19)	5.02 (3.31, 7.75)	3.59 (2.55, 5.13)	3.03 (2.27, 4.11)
Likelihood ratio negative (95% CI)	0.59 (0.51, 0.67)	0.55 (0.47, 0.64)	0.47 (0.39, 0.56)	0.47 (0.39, 0.57)	0.42 (0.33, 0.52)

Table 5. Area under the ROC curve of the 5 GDx parameters and the GDx 400.

GDx	Area	95% CI
AVE	0.583	0.524 - 0.642
SA	0.660	0.603 - 0.717
IA	0.673	0.616 - 0.729
EA	0.620	0.562 - 0.678
EM	0.725	0.673 - 0.778
GDx #	0.732	0.678 - 0.786

higher than the individual GDx parameters studied. It also had a higher positive likelihood ratio (Table 4).

DISCUSSION

Issues relating to GDx measurements

This study shows that the mean values of the five GDx parameters studied were lower in the glaucoma group than in the normal group. But the separation of the glaucoma from the normal was not clear-cut. Overlap of values was present. The ROC curves generated for the five GDx parameters and the GDx number showed curves that were

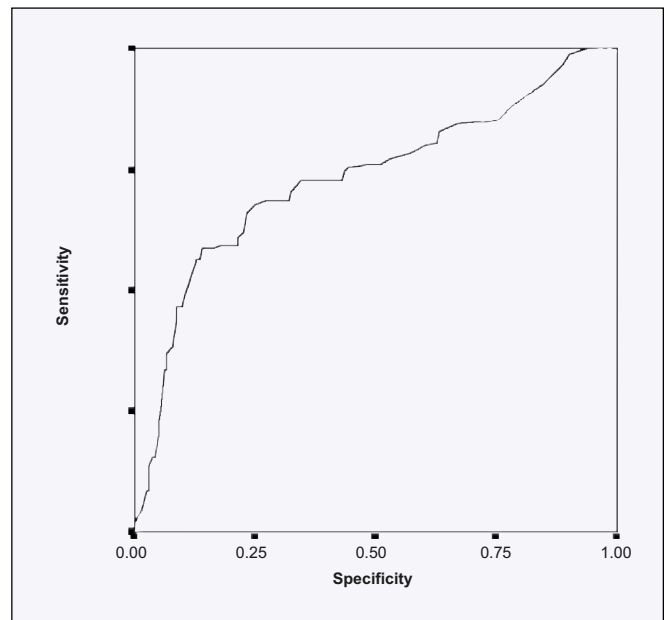


Figure 1. ROC curve of the GDx nerve-fiber analyzer.

closer to the diagonal line running from lower left to upper right, indicating that the GDx nerve-fiber analyzer did not adequately discriminate between those with and without the disease. Tests that discriminate well will show that as the sensitivity progressively goes down (the cutoff point is lowered) there is little or no loss in specificity until high levels of sensitivity are achieved. The area under the ROC curve would be much higher and closer to 1.

Most overlaps in values were between suspected glaucoma and early glaucoma cases when the study participants were further subdivided into normal, suspected glaucoma, early, moderate, and advanced glaucoma.⁹ These results were in agreement with other studies¹⁻⁵ showing that the GDx had difficulty differentiating suspected glaucoma from early glaucoma.

Issues relating to validity

Validity, or accuracy, is the degree to which the results of a measurement correspond to the true state of the phenomenon being measured. A simple way of looking at the relationship between a test's results and the true diagnosis is the two-by-two table. The test is considered to be either positive (abnormal) or negative (normal) and the disease is either present or absent.

There are four possible interpretations of test results, two of which are correct and two wrong. The test gives the correct answer when it is positive in the presence of disease or negative in the absence of disease. On the other hand, the test will be misleading if it turns out positive, even when the disease is absent (false positive) or negative when the disease is present (false negative). The results of this study showed that at best the five GDx parameters, when used individually, are able to predict correctly 60% of positive or negative test results. But when the machine is considered as a whole, the positive predictive value can be increased to 77% and the negative predictive value to 69% at a cutoff level of 50.

Caution must be exercised in interpreting diagnostic test results. The gold standard used in comparing test results must be known. The choice of a gold standard in assessing the sensitivity and specificity of a new instrument for the diagnosis of glaucoma poses several problems. Each of the tools employed in making the diagnosis of glaucoma involves looking at different aspects of the disease. In evaluating the optic-nerve head, one looks for the presence of structural damage. In visual-field testing, one looks at the functional damage. Structural damage in the ONH, as exemplified by increased cupping with loss of the neuroretinal rim, corresponds to functional damage in the visual field with characteristic glaucomatous defects. However, early visual-field defects may not be seen on SAP until enough ganglion cells (more than 40%)¹⁰ have been damaged, indicating that structural and functional

damage in the early stage of the disease is not linear.

Studies have shown that structural damage generally precedes functional damage.¹⁰⁻¹¹ Comparing findings in the ONH or visual field solely is, therefore, not adequate. When both features were combined and used to make a diagnosis, the sensitivity and specificity rose. Most studies in the last few years incorporated both aspects of the disease in making a diagnosis. Thus, the more appropriate choice of a gold standard by which an instrument can be compared with is to use all available information and tools—a battery of glaucoma tests that the glaucoma expert uses—to make a diagnosis. The glaucoma expert integrates all test results and arrives at the diagnosis of whether glaucoma is present or not.

In this study, the consensus grading of two glaucoma experts was used as the gold standard. They graded the optic-disc features and interpreted the visual-field results.

The five GDx parameters generated by the GDx 400 are indices of the “double-hump” profile of the RNFL and are indirect measures of the RNFL thickness using a scale ranging from 0 to 140. How well the five GDx parameters correlate to the true RNFL thickness (measured in microns) is unknown. The considerable overlap in values for the different groups can be due to any or a combination of the following conditions:

1. Incomplete neutralization of the corneal birefringence. The GDx 400 utilized a fixed corneal compensator. It assumes all eyes have a corneal polarization axis of 15 degrees nasally downward and a corneal polarization magnitude of 60 nm.¹² Recent studies showed that approximately 30% of eyes do not assume this configuration leading to variable results due to incomplete neutralization of the effect of corneal birefringence.¹³⁻¹⁴ Structures in the eye that exhibit major birefringence are the RNFL, lens, and the cornea. Incomplete neutralization of the effect of the lens and the cornea can result in increased birefringence that may be incorrectly attributed to that of the RNFL. In some of the eyes in this study, the GDx nerve-fiber analyzer may be measuring the corneal birefringence in addition to the RNFL birefringence.

2. There is a wide spectrum of glaucoma damage. Structural and functional damages in glaucoma do not correspond all the time.¹⁰⁻¹¹ Studies have shown that structural damage precedes functional damage; that it takes about 40 to 50% ganglion-cell loss before repeated functional damage is detected on SAP.¹⁰ This discrepancy between structure and function can be seen in the early stage of glaucoma wherein there may already be nerve-fiber-layer thinning, a structural change, but no visual-field changes yet on SAP. Or in the more advanced glaucoma wherein structural changes are far advanced yet large portions of the visual field may still be intact and vice versa.

3. The normative databases to which the GDx parameters were compared were mostly from multicenter studies done in the United States. The values were largely obtained from Caucasian eyes and may not reflect the normal values for Filipino eyes. The study by Poinoosawmy et al.⁴ showed age differences in RNFL thickness between normal white patients and Afro-Caribbeans but no data for Asians as the number of subjects was too small.

Reported sensitivities and specificities of the GDx400 vary depending on the parameters and cutoff points used. Tjon-Fo-Sang and Lemij⁶ used the 2.5 and 97.5 percentiles for the superior/inferior (S/I) ratio obtained from the retardation graph as the cutoff between normal and glaucoma. They reported sensitivity and specificity greater than 90%. Tribble et al.⁷ used the number of GDx parameters that were abnormal (i.e., 3 or more abnormal parameters considered glaucoma). The study also used the GDx number to denote the probability of abnormality in glaucoma, and had sensitivities of 57% for early, 71% for moderate, and 81% for severe glaucoma when specificity was 89%. Our results are in agreement with the latter lower sensitivities.

The GDx number assigned to each study eye by the machine was compared with the diagnosis made by the glaucoma experts. Using the cutoff level of 71, the sensitivity of the analyzer was only 45.4%. This means that the GDx system was able to detect glaucoma in less than half of the patients even though it showed a specificity of almost 92%. If the GDx would be used as a diagnostic tool to detect glaucoma, higher sensitivities are required.

To decrease false-negative errors and, therefore, increase the sensitivity at the expense of specificity, the cutoff level of the GDx number may be decreased (Table 4). If the cutoff level were lowered by 10 units, the sensitivity would increase by 13% to 58.5% with only a slight decrease in specificity (87.8%). If the cutoff level were lowered by 20 units, the sensitivity increased to 67.4% and the specificity lowered to 77.8%. There will be more false-positive errors at the expense of increasing the sensitivity level to detect early cases.

In glaucoma, detecting the disease early with continued monitoring means a decreased chance of blindness over the long term. A choice has to be made whether to *catch* all glaucoma cases early by lowering the sensitivity (when used as a screening tool), or to *maintain* good specificity (when used as a diagnostic tool). This choice will depend on the prevalence of glaucoma in the setting where the GDx machine is to be used. Positive results, even for a very specific test, when applied to patients with a low likelihood of having the disease, will be largely false positives. Similarly, negative results even for a very sensitive test, when applied to patients with a high chance of having the disease, are likely to be false negatives.

Thus, the more sensitive a test is, the better will be its negative predictive value, and the more confident the clinician can be that a patient with a negative test result does not have the disease being sought. Conversely, the more specific the test is, the better will be its positive predictive value.

One also has to consider the effect of labeling a person "glaucoma suspect" or "with glaucoma," both for economic (cost of follow-up visits and the different glaucoma tests) and psychological reasons (the stigma of the disease and fear of blindness).

Once the diagnosis has been made, the question of when to treat comes in. Management of the condition is lifelong and may involve long-term use of expensive glaucoma medications. Hence, in a diagnostic tool, a higher specificity over sensitivity is preferable since falsely labeling a patient with glaucoma has long-term consequences.

Limitations of the study

Gold standard. Standard achromatic perimetry may not be sensitive enough to detect early glaucoma damage. Newer perimetric tests, such as the short wavelength automated perimetry (SWAP)¹⁵⁻¹⁶ and the frequency doubling perimetry,¹⁷ have been reported to detect early glaucomatous changes five years before they were evident in SAP. They may replace SAP and if so would certainly be included among the gold standards in detecting the presence or absence of glaucoma.

Variable corneal compensator. The GDx 400 used a fixed corneal compensator in correcting for the effect of corneal birefringence. For eyes with corneal polarization axis and magnitude different from that of the machine, increased birefringence may occur that may incorrectly be attributed to that of the RNFL. Newer version of the SLP (GDx Access, Laser Diagnostic Technologies, San Diego, CA, USA) that can neutralize the corneal polarization axis for each eye using continuous corneal compensator,¹³ will improve the ability of this technology in detecting early glaucoma.

Normative values for Filipino eyes. Obtaining normative values specific for Filipino eyes whereby eyes tested can be compared with will certainly be advantageous since there may be racial differences in the thickness of normal RNFL.

Currently, the GDx 400 nerve-fiber analyzer is primarily used as a screening tool to detect the presence or absence of glaucoma. Its accuracy can be improved with use of the continuous corneal compensator to correct for the effect of corneal and lens birefringence. The newer version of the machine is likely to have more precise measurements with less overlap of values, leading to its use as a diagnostic tool to detect early glaucoma.

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ORIGINAL ARTICLE

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Reliability analyses of the GDx nerve-fiber analyzer

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ABSTRACT

Objectives

The scanning laser polarimetry, exemplified by the GDx 400 (Laser Diagnostic Technologies, San Diego, CA, USA) nerve-fiber analyzer, allows noninvasive quantitative assessment of the retinal nerve-fiber layer. This study determined the reliability of the GDx 400 in taking repeat measurements by different operators and at different sessions in a sample of normal and glaucoma patients.

Methods

Patients with and without glaucoma underwent a complete eye evaluation, automated achromatic perimetry, scanning laser polarimetry, and optic-disc photography. Retinal nerve-fiber layer (RNFL) measurements were obtained for each group of patients by two trained operators who were masked as to the status of the study eye. Four measurements were obtained for each study eye in the same session and in another session. Reliability measures using intraclass correlation coefficient of five preselected GDx parameters were obtained.

Results

The study recruited 355 patients (171 normal, 184 glaucomatous) ages 30 to 78 years. Intraclass correlation coefficients within operator same session (0.84-0.95), within operator different sessions (0.78-0.93), between operators same session (0.79-0.94), and between operators different sessions (0.80-0.94) were excellent. The reliability measures for the second session (0.79-0.94) were higher than for the first session (0.79-0.87) even for measurements taken by the same operator.

Conclusion

The GDx 400 nerve-fiber analyzer has good reliability measures and can be used to monitor changes in the RNFL thickness over time. Change in measurements exceeding 20% from baseline should be considered as possible progression.

Key words: *Glaucoma, Retinal nerve-fiber layer, Nerve-fiber analyzer, Scanning laser polarimetry*

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THE SCANNING laser polarimetry (SLP), exemplified by the GDx 400 (Laser Diagnostic Technologies, San Diego, CA, USA) allows noninvasive quantitative assessment of the retinal nerve-fiber layer (RNFL). This instrument uses a diode laser in the near infrared (780 nm) to obtain RNFL thickness measurements at 65,536 retinal points in a 15-by-15-degree grid centered on the optic-nerve head (ONH).^{1,2} The polarized light emitted passes through the RNFL, undergoes a phase shift that splits into two beams of different velocities. A detector in the instrument measures the degree of phase shift. This measurement, the difference in velocity, is called retardation and is proportional to the thickness of the RNFL through which the incident light has passed. The scanning laser polarimeter uses a mathematical algorithm developed by the manufacturer eliminating the effect of the cornea and the lens as the polarized light passes through them. The measurement obtained is a measure of relative nerve-fiber-layer thickness. The correlation between retardation measurements and RNFL thickness has been shown previously in experiments with histopathological measurements in postmortem human and monkey eyes.³

In recent years, several studies have validated the principle of SLP; the normal optic nerves have a typical double-hump configuration when the profiles of the RNFL surface height were plotted two dimensionally.^{4,5} The thickest areas of the nerve-fiber bundle are located superiorly and inferiorly, whereas the temporal areas tend to be lowest because of slight tilting of the ONH. Glaucomatous atrophy is indicated as a loss of the double-hump pattern with flattening and lowering of the RNFL surface profile.

Repeatability studies of the SLP were done on measurements taken at three different peripapillary locations.^{6,7} Coefficient of variation ranged from 3.6 to 4.1% in normal eyes and 5.7 to 10.2% in glaucomatous eyes. Precision was calculated up to 5 microns. Small sample size and failure to stratify the glaucoma group according to severity were evident. Whether the measurements were affected by the different operators who took the scanning images was not determined.

The ultimate usefulness of objective measurements using sophisticated tools still requires knowing the amount of variability inherent in their use. When the amount of "noise" present in the acquisition of these images is known, any change that is beyond the "noise level" would be considered related to the disease process. The usefulness of an instrument is to detect not only the presence or absence of glaucoma, but eventually to measure the progression of the disease process accurately and reliably over the long term.

Thus, this study determined the reliability of the GDx 400 nerve-fiber analyzer. Specifically, we determined the within-operator (intra-observer) and between-operators

(inter-observer) variability, as well as the within-session (same visit) and between-sessions (different visits) variability of the GDx in a sample of normal and glaucoma patients.

METHODOLOGY

This is a cross-sectional study among a sample of individuals with and without glaucoma. RNFL measurements were obtained for each group by two operators on the same day (session 1) and on another day (session 2). Reliability measures for five GDx parameters were obtained.

Patients seen at the Glaucoma Section of the Department of Ophthalmology of the Philippine General Hospital (PGH) and at the Eye Referral Center (ERC) were recruited based on the following criteria: age 30 to 79 years and visual acuity of at least 20/40 (6/12) or better with best correction. Those with significant media opacities as to preclude good scanning images, presence of retinopathy, or high refractive error of greater than minus 6 diopters were excluded. Only one eye per patient was included in the study.

The study was conducted according to the tenets of the Declaration of Helsinki. All subjects gave informed consent. The study was also approved by the Ethics Committees of the PGH, the University of the Philippines College of Medicine, and the Eye Referral Center.

Each patient underwent complete eye evaluation, automated threshold perimetry 30-2 (Octopus 101, Bern, Switzerland or Humphrey HFA I 630, San Leandro, CA, USA), scanning laser polarimetry (GDx 400), optic-disc photography (Canon 60UVI fundus camera, Tokyo, Japan).

SLP measurements

The patient faced the optoelectronic scan head of the GDx 400 with the pupil in undilated state, and fixated on an external target with the eye not being examined. After the operator has properly focused a ring-shaped target onto the iris and centered the target on the patient's pupil, a live fundus image was seen on the liquid-crystal-display monitor. The intensity of the illuminating laser light was adjusted to achieve appropriate fundus illumination. A complete scan consisting of 65,536 individual retinal locations (256 x 256 pixels) with a field of view of 15° was obtained. The acquisition time was 0.7 second per image. Immediately after acquiring and storing the data in a personal computer, a computer algorithm calculated the amount of retardation at each measured retinal position and expressed it as the RNFL thickness. A retardation map described the change in the state of polarization (retardation) at each location within the field of view. Processing time was approximately 15 seconds.

The RNFL images were obtained by two trained and

experienced operators. They were masked as to the status of the study eye. At the first session, two images were obtained by each of the operators, total of four images for the study eye. Within one week, the second set of images was obtained by the same two operators.

The RNFL measurements stored in the computer were recalled for analyses. The retardation (in degrees) was measured within a 10-pixel-wide band located concentrically with the disc margin at 1.7 disc diameters. The optic-disc margin was approximated by a circle or ellipse placed around the inner margin of the peripapillary scleral ring by the experienced operator. The retardation map was divided into four retinal regions: a superior and an inferior region of 120 degrees each, a temporal region of 70 degrees, and a nasal region of 50 degrees. Mean absolute retardation was calculated for the overall peripapillary retina (360°), superior (180°) and inferior retina (180°), temporal (70°) and nasal (50°) retina. Several GDx parameters were calculated by the computer. For the purpose of this study, the reliability of the following five parameters that give the best sensitivity based on previous studies⁸ were evaluated:

1. Average thickness (AVE) – the average of all of the thickness measurements in the image;
2. Superior average (SA) – the average of the 1,500 thickest points in the superior quadrant;
3. Inferior average (IA) – the average of the 1,500 thickest points in the inferior quadrant;
4. Ellipse average (EA) – the average of the thickness measurements along the ellipse;
5. Ellipse modulation (EM) – the difference between the thickest and thinnest areas along the ellipse.

Main outcome measures

The reliability of each of the five GDx parameters was determined for the two operators who took the RNFL images. Within-operator (intra-observer) (comparison of images taken by the same operator of the same eye) and between-operators (inter-observer) (comparison of images taken by different operators of the same eye) reliability measures were obtained. Comparison of images taken at two different sessions within one week where there is no expected clinical change was determined. Within-session (comparison of images of the same eye taken on the same visit) and between-sessions (comparison of images of the same eye taken at two different visits) reliability measures were obtained. Intraclass correlation coefficients were obtained to assess the agreement of RNFL measurements under each of the following conditions:

- a. within-operator (intra-observer) within-session
- b. within-operator (intra-observer) between-sessions
- c. between-operators (inter-observer) within-session
- d. between-operators (inter-observer) between sessions

Statistical analysis

The intraclass correlation coefficient ρ is defined by the following equation:

$$\rho = \frac{MS_{B-pt} - MS_{W-pt}}{MS_{B-pt} + (m_0 - 1) MS_{W-pt}}$$

Where

MS_{B-pt} = between-patient mean square difference

MS_{W-pt} = within-patient mean square difference

m_0 = number of ratings, in this case 2 (sessions 1 and 2)

The mean square difference is the sum of the squares divided by the degrees of freedom. ρ estimates the percentage of total variance due to the between-patient component. A high value of ρ suggests the “noise” of the measurement method is low relative to the total variance in the population.⁹

Table 1. Demographic and visual characteristics of patients (n = 355).

	Without Glaucoma (n = 171)	With Glaucoma (n = 184)
Age (years)		
Mean	55	60
SD	11.0	10.7
Male:female ratio	66:105	78:106
Visual Acuity		
Mean	0.92	0.84
SD	0.21	0.26
Refraction (spherical equivalent)		
Mean	0.15	0.17
SD	1.72	1.74
IOP (mm Hg)		
Mean	13.4	15.5
SD	3.5	5.6
Visual-Field Mean Sensitivity (decibels)		
Mean	22.72	16.93
SD	4.85	8.46
Visual-Field Mean Defect (decibels)		
Mean	4.6	8.98
SD	4.67	8.17
Loss Variance (decibels)		
Mean	17.03	25.91
SD	18.56	24.38
Vertical Cupping		
Mean	0.55	0.70
SD	0.14	0.20
Horizontal Cupping		
Mean	0.53	0.68
SD	0.14	0.20

RESULTS

Between July 2000 and July 2002, 355 patients (144 males, 211 females) were recruited into the study. The mean age was 58 years. Mean visual acuity was 20/25 (6/7.5) (0.9). Mean IOP was 14.5 mm Hg. The characteristics of the included patients in each group are shown in Table 1. Only 227 (64%) patients came back for repeat RNFL measurements.

Reliability analysis

The intraclass correlation coefficient ρ , which measures the consistency or agreement of values within cases, was excellent for the five parameters for within-operator within-session reliability measures (Table 2) and for within-operator between-sessions reliability measures (Table 3). The EM parameter has slightly lower ρ compared with the other parameters.

Good intraclass correlation coefficients (ρ) were obtained for all GDx parameters for between-operators within-session reliability measures (Table 4). The EM parameter has slightly lower ρ compared with the other parameters. The inter-observer same session reliability measures were also higher for the second session than the first session.

Between-operators between-sessions reliability measures showed good ρ for all parameters with all values above 0.8 (Table 5). This means that repeated measurements taken by different operators on different days for the same patient were reliable.

DISCUSSION

Since the GDx nerve-fiber analyzer was introduced, it has been promoted as a screening tool for the detection of glaucoma. Several studies,¹⁰⁻¹³ however, showed considerable overlap of values of the GDx measurements such that there was no clear-cut separation between normal and glaucoma eyes. More recent studies^{8, 11-14} showed lower sensitivity and specificity values for the GDx analyzer than originally demonstrated.¹⁵ Recent validation studies^{11, 16} indicated that it was more suited for documenting established glaucoma rather than for detecting early glaucoma. It is for this reason that repeatability studies are needed to determine if the GDx 400 can monitor glaucoma reliably over the long term. Since repeat measures are involved, it is essential that we know the amount of variability present that is related to the process of taking the measurements.

Variability in repeat measurements can occur when different operators take the images or when images are taken at different sessions even by the same operator. Our results showed excellent ρ for the five GDx parameters when images were taken by the same operator at the same session (Table 2) or at different sessions (Table 3). Excellent ρ values were also obtained by different operators at

Table 2. Within-operator (intra-observer), within-session (same session) reliability measures taken during the first session.

GDx Parameters	Operator 1 (n = 355)		Operator 2 (n = 355)	
	ρ^*	95%CI**	ρ^*	95%CI**
AVE	0.95	0.94-0.96	0.94	0.93-0.95
SA	0.95	0.93-0.96	0.94	0.93-0.95
IA	0.93	0.92-0.95	0.94	0.93-0.95
EA	0.94	0.93-0.95	0.94	0.93-0.95
EM	0.84	0.81-0.87	0.80	0.76-0.83

* intraclass correlation coefficient
** confidence interval

Table 3. Within-operator (intra-observer), between-sessions (two different sessions) reliability measures.

GDx Parameters	Operator 1 (n = 227)		Operator 2 (n = 227)	
	ρ^*	95%CI**	ρ^*	95%CI**
AVE	0.93	0.91-0.94	0.88	0.86-0.91
SA	0.93	0.92-0.95	0.90	0.88-0.92
IA	0.92	0.90-0.93	0.92	0.90-0.93
EA	0.93	0.91-0.94	0.88	0.85-0.90
EM	0.78	0.74-0.82	0.78	0.74-0.82

* intraclass correlation coefficient
** confidence interval

Table 4. Between operators (inter-observer), within-session (same session) reliability measures taken during the first session.

GDx Parameters	Session 1 (n = 355)		Session 2 (n = 227)	
	ρ^*	95%CI**	ρ^*	95%CI**
AVE	0.84	0.82-0.86	0.94	0.93-0.95
SA	0.85	0.83-0.87	0.94	0.93-0.95
IA	0.87	0.85-0.89	0.92	0.91-0.94
EA	0.85	0.83-0.87	0.93	0.91-0.94
EM	0.79	0.75-0.82	0.79	0.75-0.82

* intraclass correlation coefficient
** confidence interval

Table 5. Between-operators (inter-observer), between-sessions (two different sessions) reliability measures.

GDx Parameters	ρ^*	95% CI**
AVE	0.93	0.92-0.95
SA	0.94	0.92-0.95
IA	0.93	0.91-0.94
EA	0.93	0.91-0.94
EM	0.80	0.76-0.83

* intraclass correlation coefficient
** confidence interval

the same session (Table 4) and at different sessions (Table 5). Almost all values were 0.8 or better and considered excellent.⁹ Hence, the GDx 400 showed that it can reliably take RNFL images in the same eye by different operators at different sessions. Learning effect can also improve the reliability measures; measurements taken during the second session, within one week from the first session where there is no likelihood of a clinical change in the eye, have higher ρ than those of the first session (Table 4). During the first session, each patient underwent multiple tests that lasted two and one half hours. The RNFL

measurements were obtained toward the end of the session and patients already showed signs of fatigue. The second session, moreover, lasted less than one hour and the only test done was a repeat RNFL measurements. Thus, one way to improve the reliability of the GDx measurements is to ensure that patients know what the procedure involves.

One of the recommendations of the Association of International Glaucoma Societies (AIGS) is using digital imaging as a clinical tool to enhance and facilitate assessment of the optic nerve and RNFL in the management of glaucoma.¹⁷ Moreover, automated analyses of the results should use appropriate databases in identifying abnormalities consistent with glaucoma. In recent years, different imaging techniques^{5, 6, 8, 10, 18-21} capable of documenting and quantifying the optic-nerve-head features and the RNFL were developed. These imaging technologies may be complementary and may detect different abnormal features in the same patients.¹⁷ Hence, they should not probably be compared against each other; rather, they should be used to enhance the clinical decision-making of the ophthalmologist in monitoring the disease process.

Good repeatability of measurements is a prerequisite for following any change in measurement over time. The good intraclass correlation coefficients obtained for the nerve-fiber analyzer for different operators and at different sessions showed that this machine can be used for repeat measures over time to determine any progression of the disease. Variations in measures can be obtained in the same eye using the same instrument and by the same operator. These variations are called fluctuations and can be found in any eye being measured. Some common examples are the short- and long-term fluctuations found in visual-field tests. For the different GDx parameters, there are also fluctuations in measurements over time. These fluctuations usually consist of the variability measured with regard to the different operators and different sessions. For a change to be considered "real," the normal fluctuations in measurements must be exceeded. In this study, if fluctuations in measurements should exceed 20% from baseline, the possibility of disease progression should be considered. Future studies on the long-term use of the GDx machine with follow-up GDx measurements will provide answers as to the amount of "noise" that must be exceeded to consider the change in measurements as progression of the disease.

Possible sources of bias in this study include patient selection and performance bias. Patients included in the study were those who could undergo multiple eye tests for several hours and, therefore, tended to be much younger (mean age of 58 years) than the general population of elderly where most established glaucoma is found. In addition, the older population has more difficulty per-

forming reliable visual-field tests and is also expected to do less well at the GDx 400. The reliability of the GDx test results, however, is influenced less by patient's cooperation, as the testing procedure is much shorter and involves only good fixation. In our study, there was no difference in the reliability measures of the normal (mean age of 55 years) and the glaucoma (mean age of 60 years) patients. All the glaucoma patients in this study have 20/40 (6/12) or better vision. Patients with advanced glaucoma and poorer visual acuity may do less well with greater variability than those shown in this study. Caution in the interpretation of follow-up GDx measurements in the elderly must be exercised even in the presence of variability greater than 20% of baseline since these may still be attributed to the patient. Operators who took the measurements in this study were likely to be giving more time and effort in the acquisition of the images more than they normally do for clinic patients.

This study did not look into the variability of using other GDx machines of the same model (variability between machines) nor of a different model such as the GDx Access (an improved version).²²⁻²³ Prudence dictates that adequate baseline should be obtained for all patients. The optimum number of repeat measurements as baseline has not been determined and is beyond the scope of this study. In the long-term follow-up of glaucoma patients, whenever there is a change in the GDx machine, new baseline studies should be obtained.

In summary, the GDx 400 nerve-fiber analyzer has good reliability and can be used to monitor changes in the RNFL thickness over time. Change in measurements exceeding 20% from baseline should be considered as possible progression.

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ORIGINAL ARTICLE

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Correlation of central corneal thickness and Goldmann applanation tonometry among Filipinos

ABSTRACT

Objective

To determine the distribution of central corneal thickness (CCT) among Filipinos and to correlate CCT with intraocular pressure (IOP).

Methods

A prospective cross-sectional study was performed among Filipino patients consulting at the General Ophthalmology Clinic of the Philippine General Hospital. They underwent a comprehensive eye examination. CCT obtained by ultrasonic pachymetry and IOP by Goldmann applanation tonometry were correlated using linear regression analysis. Factors affecting CCT measurements were analyzed by ANOVA.

Results

Two hundred twenty two eyes of 112 patients were included in the study. CCT ranged from 451.0 μ m to 653.6 μ m with a mean of 531.5 μ m \pm 33.8 μ m. There was a significant linear correlation between CCT and IOP ($r = 0.63$). The IOP was noted to rise by 4.3 mm Hg/100 μ m CCT.

Conclusion

The CCT among Filipinos is normally distributed and is comparable to the distribution obtained by metaanalysis of worldwide data. The study also found a direct correlation between CCT and IOP among Filipinos.

Key words: *Applanation tonometry, Central corneal thickness, Glaucoma, Intraocular pressure*

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ACCURATE measurement of intraocular pressure (IOP) is essential not only in the diagnosis and management of glaucoma, but also in the postoperative monitoring of those who have undergone intraocular surgery. Currently, Goldmann applanation tonometry is the gold standard for clinical measurement of IOP. It works on the principle that the pressure inside an ideal sphere is equal to the force necessary to flatten its surface, divided by the area of flattening.¹

In calibrating this tonometer, Goldmann assumed a standard central corneal thickness (CCT) of 0.55 mm.¹ He predicted that variations from this standard corneal thickness, which he assumed to be rare, would be a source of error in measuring IOP. Currently, there is accumulating evidence that Goldmann's theoretical prediction is correct.

Several studies involving simultaneous IOP measurements by applanation tonometry and by manometry have demonstrated that thicker corneas yield an overestimation of IOP by applanation.²⁻⁴

Population-based studies have also demonstrated a positive correlation between CCT and IOP measured by Goldmann applanation tonometry^{5, 6} or Tono-Pen.⁷ A recent metaanalysis of IOP measured by applanation and CCT, which pooled 133 data sets, revealed a statistically significant correlation between the two.⁸ Studies involving patients who have undergone Photorefractive Keratectomy (PRK)⁹⁻¹³ and Laser in Situ Keratomileusis (LASIK)¹⁴ have demonstrated a corresponding drop in postoperative IOP with the cornea ablated.

Numerous studies have shown that patients diagnosed with ocular hypertension have significantly thicker corneas compared with normal subjects, suggesting that IOP in this group of patients is being overestimated.¹⁵⁻¹⁸ Similarly, patients diagnosed with normal-tension glaucoma have thinner corneas than normal subjects, suggesting that IOP in this group of patients is being underestimated.^{16, 18, 19, 20}

Given these, several authors have recommended that CCT be considered in interpreting IOP or adjustments be made in IOP based on CCT.^{2-5, 7, 11, 13-15, 17, 18, 21, 22}

To date, there are no published studies of CCT among Filipinos. It may be inappropriate to apply studies on IOP and CCT done in other countries to the Philippine setting because several studies have demonstrated interracial differences in the range of CCT and factors affecting these values.^{7, 8}

This study determined the following among Filipinos: the distribution of CCT, the correlation between CCT and IOP, and the association between CCT and other factors such as age, gender, diabetes, thyroid disease, hypertension, trauma, eye surgery, and family history of glaucoma.

METHODOLOGY

This is a prospective cross-sectional study involving Filipino patients seen consecutively at the General Ophthalmology Clinic of the Philippine General Hospital Outpatient Department from October 17 to 19, 2000. Patients over 10 years old with normal IOP, optic-nerve head, and cornea were included in the study. Patients with the following findings were excluded: glaucoma, use of glaucoma medication for the past month, intraocular surgery for the past 3 months, intraocular or retrobulbar tumor, contact lens use for the past 1 month, uveitis, retinal detachment, conjunctivitis, corneal ulcer, corneal dystrophy, and corneal refractive surgery. Patient consent was obtained.

Patients included in the study were seen by a single examiner (PG). A case-report form was completed indicating demographic and other factors that could affect IOP and CCT. Proparacaine (Alcaine, Alcon, Fort Worth, TX, USA) was given as a topical anesthetic before IOP and CCT measurements were taken. IOP was measured twice using a Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland) with both measurements within 1 mm Hg. The mean of the two measurements was then recorded. CCT was measured 10 times until all 10 measurements had a standard deviation (SD) of less than 5 using an ultrasound pachymeter (Bio & Pachy Meter AL-2000, Nishi-ku, Nagoya, Japan). Both instruments were disinfected with 70% isopropyl alcohol between each use. The calibration of both instruments was checked daily prior to the start of each study session.

Statistical analyses were performed using Epi Info version 6.02c (Centers for Disease Control and Prevention, Atlanta, GA, USA). *P* values less than 0.05 were considered statistically significant. For all statistical tests, the mean of the ten CCT measurements was used. The correlation between average CCT and IOP, and between CCT and age were determined by linear regression. The effect of gender; family history of glaucoma; diseases such as diabetes mellitus, systemic hypertension, and thyroid disease; trauma; and eye surgery on CCT was determined by analysis of variance (ANOVA). The right and left eyes were analyzed separately since IOP and CCT measurements between eyes are interdependent.

RESULTS

The study included 222 eyes of 112 patients of whom 36 were male and 76 were female. Two patients had 1 eye where IOP and CCT could not be measured because of corneal irregularity secondary to trauma. The patients' ages ranged from 16 to 86 years with a mean of 52.3 ±17.5 years. Most of the patients were in the 51- to 70-year age group (Figure 1). CCT ranged from 451.0 μm to 653.6 μm with a mean of 531.5 ±33.8 μm (Figure 2). The IOP

ranged from 11 mm Hg to 21 mm Hg with a mean of 16.2 ± 2.3 mm Hg. A direct linear correlation was found between CCT and IOP ($r = 0.63$). The IOP was noted to rise by 4.3 mm Hg/100 μ m CCT (Figure 3).

No significant correlation was found between CCT and age, gender, diabetes, thyroid disease, hypertension, trauma, eye surgery, or family history of glaucoma ($p > 0.05$). Neither was there a significant relationship between IOP and these factors ($p > 0.05$).

DISCUSSION

There is no general consensus on what is the average normal CCT. It has been estimated to range from 518 μ m²⁴ to 580 μ m.²¹ A recent metaanalysis of measured CCT in normal eyes pooled from 300 data sets worldwide reported a mean of 534 ± 31 μ m.⁸ Our study population had a comparable mean CCT of 531.5 ± 33.8 μ m. The CCT values were distributed normally (Figure 2).

Our study population also showed a direct correlation between CCT and IOP measured by Goldmann applanation tonometry ($r = 0.63$). An increase of 4.3 mm Hg per 100 μ m of CCT increase was noted. This correlation is lower compared with results reported in manometry studies. Ehlers et al.² reported a 5 mm Hg rise for every 70 μ m CCT (7.14 mm Hg/100 μ m CCT) while Whitacre et al.⁴ predicted an error of 3.5 mm Hg for every 70 μ m CCT (5 mm Hg/100 μ m CCT).

Compared with population-based studies by Dohadwala et al.,⁷ Foster, et al.,⁵ and Wolfs et al.,⁶ our computed slope for IOP rise for every μ m is steeper. Dohadwala et al.⁷ reported only a 2 mm Hg increase per 100 μ m CCT. Their study, however, used a Tono-Pen to measure IOP. In contrast, Foster et al.⁵ used an optical pachymeter and reported a 1.8 mm Hg/100 μ m slope for right eyes and 2.4 mm Hg/100 μ m for left eyes. Wolfs et al.⁶ reported a rise of 1.9 mm Hg/100 μ m. This study, however, only included patients aged

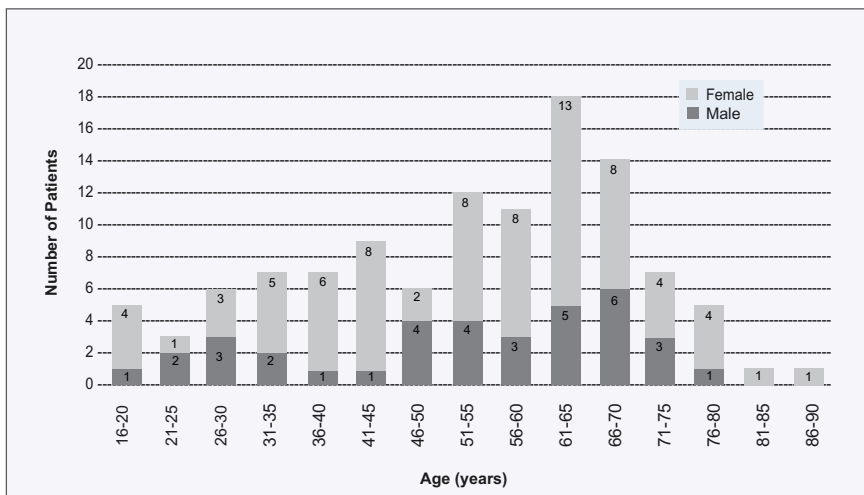


Figure 1. Age distribution of patients (n = 112).

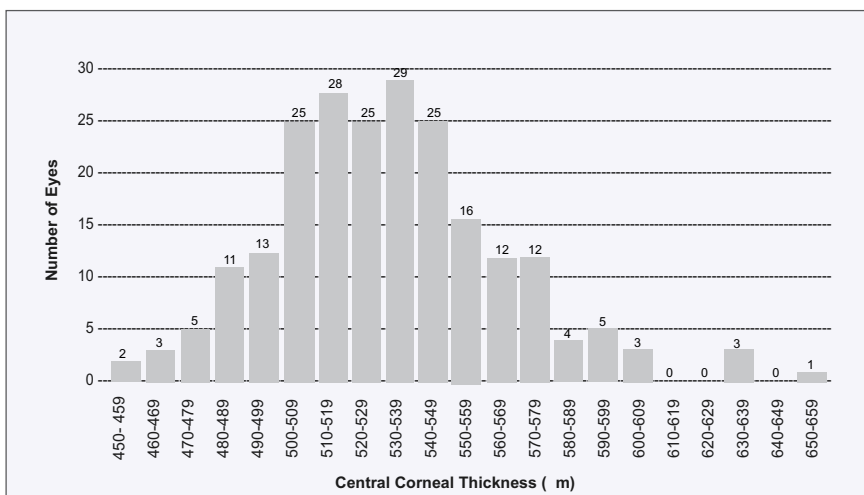


Figure 2. Distribution of central corneal thickness among Filipinos (n = 222).

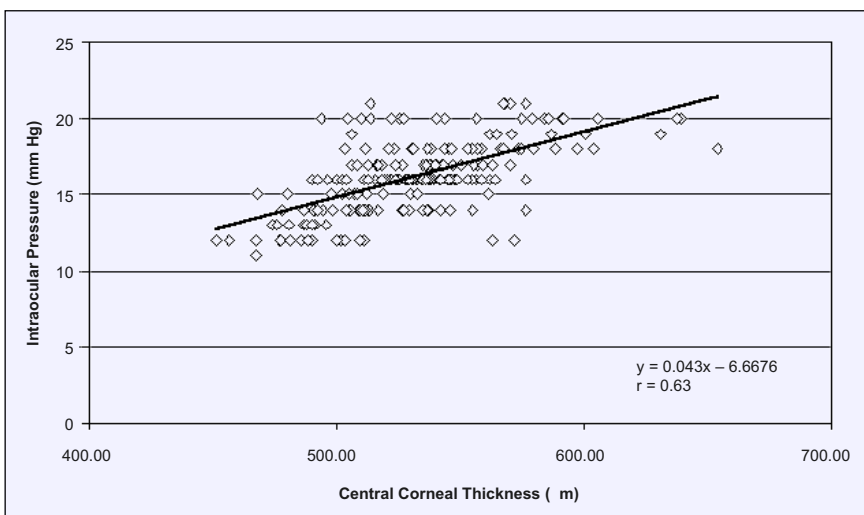


Figure 3. Scatterplot of central corneal thickness and intraocular pressure (n = 222).

55 or older (Table 1). Variations in the results obtained may also be partly explained by the differences in the number of eyes examined.

Dohadwala et al.⁷ reported a significant difference in CCT among Asians, Blacks, and Caucasians. It is likely that interracial variation could partly explain the difference in the magnitude of the relationship observed between other studies and our study. Differences in instrumentation and characteristics of the study population are also possible causes.

Other studies have reported that factors such as age,²⁵⁻²⁷ gender,^{7, 28, 29} hypertension,^{7, 30-32} diabetes,^{7, 20, 28, 33, 34} and family history of glaucoma^{28,35} have relationships to IOP and/or CCT. Our study, however, did not show any statistically significant relationship.

This study showed that CCT among Filipino patients consulting at the General Ophthalmology Clinic of the Philippine General Hospital is normally distributed and is comparable to the distribution obtained by metaanalysis of worldwide data. The study also found a direct correlation between CCT and IOP. Variation in CCT is a source of systematic error caused by the cornea's resistance to flattening. Further population-based and manometry studies with larger sample sizes are recommended to evaluate the relationship between CCT and IOP as measured by Goldmann applanation tonometry. Such studies could help generate a formula for adjusting IOP measured by applanation to compensate for variations in CCT.

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Table 1. Correlation of central corneal thickness and intraocular pressure in various studies.

Study	Increase in IOP per 70 m Increase in CCT (mm Hg)	Increase in IOP per 100 m Increase in CCT (mm Hg)
<i>Manometry studies</i>		
Ehlers, et al.	5	7.14
Whitacre, et al.	3.5	5
<i>Population-based studies</i>		
Lat-Luna, et al.	3	4.3
Dohadwala, et al.	1.4	2
Foster, et al.		
right eye	1.26	1.8
left eye	1.68	2.4
Wolfs, et al.	1.33	1.9

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ORIGINAL ARTICLE

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Comparison of outcomes of trabeculectomies using 0.4 mg/ml versus 0.2 mg/ml concentrations of mitomycin-C

ABSTRACT

Objectives

This study compared the outcomes of trabeculectomies using 0.2 mg/ml and 0.4 mg/ml mitomycin-C (MMC) and determined the factors that can predict the postoperative intraocular pressure (IOP).

Methods

A prospective, randomized, comparative study was performed involving patients undergoing trabeculectomy who were randomly assigned to either 0.2 mg/ml MMC for 4 minutes or 0.4 mg/ml for 2 minutes. The IOP, bleb characteristics, and occurrence of complications were compared. Age and gender of the patients, preoperative IOP, MMC concentration, bleb characteristics, angle status, and age of the surgery were analyzed to determine if they are predictive factors of the postoperative IOP using univariate and multivariate analyses.

Results

Seventy-four eyes of 68 patients underwent trabeculectomy: 36 eyes were treated with 0.2 mg/ml MMC for 4 minutes and 38 eyes with 0.4 mg/ml MMC for 2 minutes. There was no statistically significant difference in the mean preoperative IOP and postoperative IOP, as well as in the mean percent change in IOP ($p = 0.87$) between the 2 groups. Univariate and multivariate analyses showed the preoperative IOP ($p = 0.02$) and the type of filtering bleb (cystic $p < 0.001$; diffuse $p = 0.045$) as predictive factors of postoperative IOP. Kaplan-Meier survival curves showed no significant difference between the 2 groups at an average follow-up of 20 weeks.

Conclusion

There is no significant difference in the outcomes of trabeculectomies using 0.2 mg/ml and 0.4 mg/ml MMC. Preoperative IOP and bleb characteristics are factors predictive of successful filtration surgery.

Key words: *Trabeculectomy, Mitomycin-C, Intraocular pressure, Filtering bleb*

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THE SURGICAL management of glaucoma is an indispensable alternative in developing countries where there are limitations in medical and laser therapy. Glaucoma filtration surgery fails due to the scarring of the filtering bleb, where fibroblast proliferation from the episclera and Tenon's capsule play a significant role.¹ The use of antimetabolites has improved the success rate of glaucoma filtration surgery. Mitomycin-C is an antibiotic with antineoplastic activity, inhibiting the proliferation of fibroblasts. At present, there is no known consensus as to the ideal concentration and exposure time of mitomycin-C.²⁻¹⁷ The concentrations used in different studies ranged from 0.02 mg/ml to 0.5 mg/ml. The most commonly used concentrations are 0.2 mg/ml and 0.4 mg/ml. Exposure time varies from 30 seconds to 5 minutes, with the latter as the most common.

This study compared the outcome of trabeculectomies using 0.4 mg/ml MMC (Mitomycin C Kyowa, Tokyo, Japan) for 2 minutes as against 0.2 mg/ml MMC for 4 minutes in terms of IOP lowering, characteristics of the filtering bleb, and incidence of complications. It also determined the factors that can predict the postoperative intraocular pressure (IOP).

METHODOLOGY

Patients seen consecutively at the Glaucoma Service of the Philippine General Hospital (PGH) between January and June 1997 were evaluated. Those who had uncontrolled IOPs, cup-disc ratio of 0.8 or worse, and on maximum tolerated medical therapy were eligible for inclusion into the study. Patients who had systemic contraindications to surgery, who could not comply with the follow-up schedule, or who refused to give their consent were excluded.

Based on the clinical diagnosis, patients requiring a filtering procedure were classified as either low risk for surgical failure (e.g. primary glaucomas) or high risk for surgical failure (e.g. congenital and developmental glaucomas, neovascular glaucoma, previous surgeries, failure of previous trabeculectomy, traumatic glaucoma, previous cataract surgery, secondary glaucoma, inflammatory glaucoma).¹⁸ Using a table of random values, each patient was assigned to either the 2 minute exposure of 0.4 mg/ml MMC or the 4 minute exposure of 0.2 mg/ml MMC. The patients and the surgeons were masked as to which MMC concentration would be used. A trabeculectomy protocol approved by the consultants of the Glaucoma Service was used.

After peribulbar anesthesia was given, a corneal bridge using vicryl 8-0 (Ethicon, Johnson & Johnson International, New Brunswick, NJ, USA), was sutured at 12:00. A superior limbal-based conjunctival flap 10 mm posterior to the limbus was created. After hemostasis and clearing of the episclera, a 3x3 mm triangular scleral flap of half

thickness was fashioned with the apex of the flap at 12:00. The flap was dissected anteriorly up to the limbal gray zone. A 3mm cut cotton sponge soaked in MMC was applied under the scleral flap. Only the assisting resident was aware of the actual exposure time and was in charge of removing the cotton sponge from the surgical field. The scleral bed was irrigated with 40 ml of balanced salt solution. A paracentesis was done at the temporal limbus and its patency tested. The anterior chamber was entered using blade 11 knife and a sclerostomy was created with 0.75 mm Kelly punch (Storz, St. Louis, MO, USA). Peripheral iridectomy was done with Vannas scissors. The anterior chamber was reformed and the filtering of fluid checked. Three 10-0 nylon sutures secured the scleral flap snugly to the scleral bed; fluid was seen to egress after lightly dabbing on the incision site with a cotton pledget. The Tenon's capsule and conjunctiva were sutured continuously and closed separately with nylon 10-0 suture. All surgeries were performed by the glaucoma fellow and the 7 senior residents who were rotating in the Glaucoma Service during that period.

The IOP before surgery and on the most recent follow-up were compared. The main outcome measure was the change in IOP. The filtering surgery was considered successful when there was at least 30% reduction of IOP from baseline. Secondary outcome measures were the type of filtering bleb and incidence of complications. The type of filtering bleb on the most recent follow-up was classified:

- cystic, if the bleb was localized, elevated, with cystic changes of the overlying conjunctiva;
- diffuse, if the border of the bleb was ill-defined, elevated with no visible changes in the overlying conjunctiva;
- vascular or congested, if the bleb was localized, elevated, and surrounded by ropy blood vessels; or
- flat, if the bleb is not elevated, difficult to discern (not visible), and there were no changes to the overlying conjunctiva.

The outcome assessors were masked as to the patient's group assignment.

Univariate and multivariate analyses using Cox proportional hazard modeling were done to determine the effects of factors such as age and gender of the patient, angle status, preoperative IOP, MMC concentration and duration in minutes of MMC application, bleb characteristics, and age of the surgery or duration of follow-up on the postoperative IOP. For variables age and sex, the unit of analysis was based on the patient for person-based covariates. For the other variables studied, the unit was based on the eye for eye-based covariates. Kaplan-Meier survival curves were determined for the two treatment groups to detect any difference in IOP change over the period of follow-up.

Table 1. Distribution of patients according to risk of surgical failure and MMC concentration.

Diagnosis	Risk	MMC Concentration	
		0.2 mg/ml	0.4 mg/ml
Primary open-angle glaucoma	Low	4	3
Chronic angle-closure glaucoma	Low	17	15
Intermittent angle-closure glaucoma	Low	2	2
Acute angle-closure glaucoma, refractory	Low	1	2
Neovascular glaucoma	High	2	3
Failed trabeculectomy	High	2	3
Developmental glaucoma	High	0	5
s/p Cataract extraction (ECCE) with PCIOL	High	1	1
s/p Combined surgery	High	0	2
Axenveld-Rieger syndrome	High	4	0
Secondary angle-closure glaucoma	High	0	2
Previous intraocular surgery (other than cataract surgery)	High	3	0
TOTAL		36	38

Table 2. Comparison of mean preoperative and postoperative IOPs in eyes treated with 0.2 mg/ml and 0.4 mg/ml MMC.

Treatment Group	Preoperative	Postoperative	Mean IOP Reduction (mm Hg) ^c	Mean % change
0.2 mg/ml	37.5 ± 13.2	14.0 ± 7.9 ^a	-18.1	-49.4 ± 6.6
0.4 mg/ml	34.4 ± 12.0	15.6 ± 8.4 ^b	-17.4	-42.9 ± 6.6

^ap = 0.002, ^bp = 0.038, ^cp = 0.873

Table 3. Distribution of types of filtering bleb and mean IOP change.

Bleb Type	Frequency	0.2 mg/ml MMC	0.4 mg/ml MMC	Mean IOP Change	95% Confidence Interval	
					Lower	Upper
Cystic	45	22 (61%)	23 (61%)	-22.575 ± 2.086	-26.744	-18.407
Diffuse	9	4 (11%)	5 (13%)	-21.152 ± 2.798	-26.740	-15.563
Vascular	9	6 (17%)	5 (13%)	-7.435 ± 2.922	-13.272	-1.598
Flat	11	4 (11%)	5 (13%)	-19.918 ± 2.974	-25.859	-13.977

RESULTS

A total of 74 eyes of 68 patients (46 females, 22 males; mean age of 51 ± 2.2 years) underwent filtering surgery between January and June 1997. Forty-three (58.1%) of these eyes were right eyes.

Forty-six eyes were classified as low risk and 28 eyes as high risk (Table 1). The two MMC concentrations studied were evenly distributed between the two surgical risk groups. Thirty-six eyes were treated with 0.2 mg/ml MMC while 38 eyes were treated with 0.4 mg/ml MMC. The mean preoperative IOP was 35.9 ± 1.47 mm Hg and the mean postoperative IOP was 14.8 ± 0.94 mm Hg (Table 2). The mean IOP change for both groups from preoperative levels was -21.1 ± 1.8 mm Hg. There was no statistically significant difference (*p* = 0.87) in mean IOP reduction between the two groups postoperatively (Table 2). The average percent change in IOP was -53.8 ± 3.3 for both groups. Fifty-five eyes (74.3%) achieved a 40% reduction

Table 4. Factors predictive of postoperative IOP (univariate analysis).

Factors Studied	Hazard Ratio	95% Confidence Interval		p Value
		Lower	Upper	
Age of patient	-5.730	-5.818	-5.642	0.211
Preoperative IOP	-0.960	-1.093	-0.827	<0.001
Diffuse bleb	-12.765	-19.233	-6.297	<0.001
Vascular bleb	-11.819	-18.293	-5.345	0.001
Cystic bleb	-14.621	-19.987	-9.255	<0.001
Mitomycin	0.541	-2.683	3.765	0.743
Neovascular glaucoma	1.295	-6.090	8.680	0.732
Duration of follow-up	8.303	8.158	8.448	0.269

Table 5. Factors predictive of postoperative IOP (multivariate analysis).

Factors Studied	Hazard Ratio	95% Confidence Interval		1/Exp (B')	p Value
		Lower	Upper		
Mitomycin C	0.271	-0.968	1.510	0.763	0.668
Age of patient	-0.005	-0.038	0.028	1.005	0.749
Diffuse bleb	-1.932	-3.818	-0.046	6.897	0.045
Vascular bleb	-0.549	-2.323	1.225	1.730	0.544
Cystic bleb	-3.201	-4.632	-1.770	24.390	<0.001
Angle closure	-0.254	-1.777	1.269	1.289	0.744
Neovascular glaucoma	1.865	-0.838	4.568	0.155	0.176
Preoperative IOP	-0.121	-0.223	-0.019	1.129	0.020

*odds ratio

from baseline IOP. Fifty-eight eyes (78.4%) achieved a 30% reduction from baseline IOP. The mean follow-up period was 19.7 ± 1.5 weeks.

The most common bleb in both treatment groups was cystic (Table 3). There was no difference in the type of bleb between the 2 groups. The different bleb types also showed differences in postoperative IOP. Flat bleb had the lowest IOP change of only 7.435 mm Hg compared to 21.152 mm Hg for diffuse bleb, 19.918 mm Hg for vascular bleb, and 22.575 mm Hg for cystic bleb (Table 3).

Complications noted were few: 3 cases of hypotony (2 in 0.2 mg/ml and 1 in 0.4 mg/ml), 4 cases of hyphema (1 in 0.2 mg/ml and 3 in 0.4 mg/ml), 1 case of flat anterior chamber (0.4 mg/ml) and 2 cases of choroidal effusion (0.2 mg/ml). There was no difference in the incidence of complications between the two groups.

Univariate analysis showed that preoperative IOP and the different types of bleb are significant predictors of IOP after filtering surgery (Table 4). In multivariate analysis, only preoperative IOP, cystic and diffuse blebs are significant predictors of postoperative IOP (Table 5). There is no evidence that MMC concentration (either the 0.2 mg/ml or the 0.4 mg/ml concentration), angle configuration, patient age, patient gender, age of the surgery in weeks are predictors of IOP after filtering

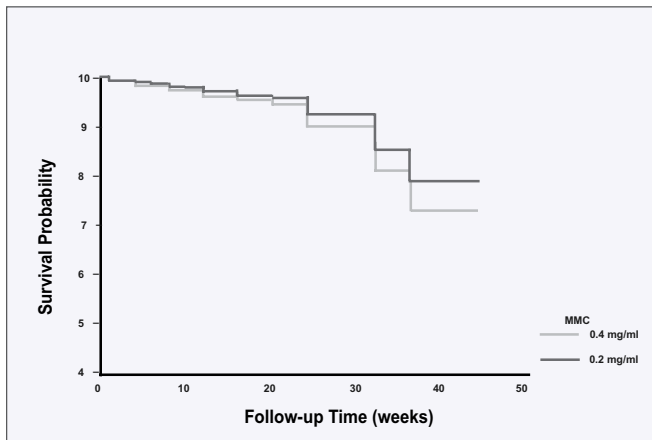


Figure 1. Kaplan-Meier survival curve of 0.2 mg/ml and 0.4 mg/ml MMC.

surgery (Table 4). Linear regression analysis showed that for every 1 mm Hg IOP rise at baseline, there is a corresponding 0.960 mm Hg reduction in IOP during the postoperative follow-up. The regression model has an R^2 of 82%, indicating that the variability of the IOP after filtering surgery is explained by the identified independent variables in the model 82% of the time.

Figure 1 shows the survival curves of the two treatment groups. The difference in survival between the groups is not statistically significant.

DISCUSSION

Mitomycin-C is one of the most frequently used antifibrotic agents in glaucoma filtration surgery. In conditions where the incidence of bleb scarring is common, resulting in a much lower success rate of trabeculectomy or a higher reoperation rate, use of an antifibrotic agent on a routine basis is justified. In the Philippines, the most common concentrations of MMC used are 0.2 mg/ml and 0.4 mg/ml, with exposure time varying from 2 to 5 minutes.

There are two factors to consider when using antifibrotic agents in glaucoma filtration surgery: the concentration of the agent and the duration of application. The strength of MMC application can be varied by either increasing the concentration, usually 0.4 mg/ml over 0.2 mg/ml, or increasing the duration of application to as long as 5 minutes. The total dose of the application can be calculated as concentration multiply by duration of exposure. In this study, we opted for keeping the total dose similar (0.4 mg/ml x 2 minutes versus 0.2 mg/ml x 4 minutes) in order to predict the factors affecting IOP control postoperatively with minimal effect of confounding factors. We compared a high MMC (0.4 mg/ml) concentration applied for a shorter duration (2 minutes) to a lower MMC (0.2 mg/ml) concentration applied for a longer duration (4 minutes) to prevent serious postoperative complications such as scleral necrosis, which

has been reported when higher doses were used.

Several investigators studied the effects of Mitomycin-C by either using a constant concentration with varying exposure time,^{8,14} a constant exposure time but varying MMC concentrations,^{6,7,9} or variable concentrations and exposure time.^{4,11} These studies showed no significant difference in the success of IOP control between the various MMC concentrations (0.2 mg/ml to 0.5 mg/ml), except for those with very low concentrations of 0.02 mg/ml⁶ to 0.1 mg/ml⁷ where the success rate was significantly lower. Varying the exposure time (2 to 5 minutes) also did not show any significant difference among the different groups. Our study similarly showed no significant difference in IOP lowering between the two groups studied at an average follow-up of 20 weeks (Table 3). The survival curves of the two treatment groups were also similar (Figure 1). However, there is a possibility that had the observation period been prolonged, there may result a significant difference between the two, especially for the period beyond 35 weeks.

The incidence of complications in this study was similar between the two treatment groups. Several studies reported a higher incidence of postoperative hypotony⁷ and hypotony maculopathy^{6,8} in those treated with higher concentrations of MMC and longer duration of exposure. Other studies^{9,11} reported no significant difference. Our study had only 3 cases of hypotony, 2 of which occurred in the 0.2 mg/ml concentration. The similarity of the total dose in the 2 treatment groups in this study may account for the no difference in the incidence of hypotony. Had the duration of exposure been varied, such as to 4 or 5 minutes for the higher concentration MMC especially in the low-risk group, the occurrence of hypotony may increase dramatically.

The univariate analysis (Table 4) of the predictive factors for postoperative IOP showed that preoperative IOP and the type of filtering bleb were the only significant predictors. Patient factors such as age and gender were not predictors indicating that MMC use during glaucoma filtration surgery is independent of the patient. Angle status or the type of glaucoma (high risk versus low risk of surgical failure) was not predictive, indicating that MMC use is independent of glaucoma type. The concentration of MMC and the duration of application were also not predictors in this study. Since the total dose of the two treatment groups was similar, the effect of MMC concentration and duration of application may have been negated. Varying the total dose as in varying the exposure time of the higher concentration MMC may have different effects on the postoperative IOP.

In the multivariate analysis (Table 5), preoperative IOP still remained a predictor of postoperative IOP. The level of preoperative IOP had an effect on postoperative IOP

or success of the filtering surgery; the higher the preoperative IOP, the greater likelihood that the filter will not fail. This is because of the definition of success rate used in this study. A higher preoperative IOP would result in a higher chance of attaining a 30% reduction of IOP. In the Cox model, for every 1 mm Hg IOP rise at baseline, there was a corresponding 0.960 or 1 mm Hg reduction in IOP during the postoperative follow-up.

In the type of filtering bleb, only diffuse and cystic blebs remained predictive in the Cox model. The more cystic the bleb (also true for diffuse), the lower the postoperative IOP. This was further supported by the mean IOP change for each type of bleb. Most of the blebs in this study were cystic (61%) with the lowest mean IOP change of 22.5 mm Hg, followed by diffuse bleb (Table 6). The vascular bleb, even though it had a large mean IOP change postoperatively, was no longer predictive of a successful filter. This could be due to the shorter follow-up (ranging from 4 to 12 weeks) occurring mostly in those with a vascular bleb. In the Cox model, an eye with a diffuse bleb has 7 times less chance of failure than a flat bleb. Eyes with vascular or cystic blebs have 1.73 and 24.4 chances of increase in probability of success, respectively, compared with a flat bleb (Table 5). Furthermore, the model showed that for every 10 mm Hg reduction from preoperative IOP, the chance of success is increased by 3.35 times ($p = 0.02$).

The regression model has an R^2 of 82%, indicating that the variability of the IOP after filtering surgery could be explained by the identified independent variables included in the model 82% of the time. Other factors, not taken into consideration in this study that may explain the other 18% of the variability are varying exposure time of the MMC concentration, varying follow-up periods, and different surgeons performing the surgery. These factors may affect the ultimate outcome in the differences between using 0.4 mg/ml over 0.2 mg/ml of MMC. Future studies should address these issues, preferably the same surgeon and the same but longer follow-up period for all

patients and varying the exposure time.

In summary, there is no significant difference observed in the outcomes of trabeculectomies using a 0.4 mg/ml of MMC at 2 minutes versus 0.2 mg/ml of MMC at 4 minutes over an average follow-up period of 20 weeks. Preoperative IOP and type of filtering bleb are factors predictive of a successful filtration surgery.

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CASE SERIES

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Treatment of ocular toxoplasmosis in pregnancy

ABSTRACT

Objectives

To describe the course of ocular toxoplasmosis during pregnancy.

Methods

This is a retrospective, noncomparative case series of four pregnant women who were treated for ocular toxoplasmosis during pregnancy.

Results

All of the participants had violent and treatment-resistant toxoplasma retinochoroiditis during pregnancy, leaving three of them with decreased visual acuity in spite of aggressive therapy. Termination of pregnancy appeared to help the recovery in two patients.

Conclusion

Pregnant state may provoke the recurrence of ocular toxoplasmosis.

Key words: *Toxoplasmosis, Retinochoroiditis, Uveitis, Pregnancy*

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TOXOPLASMOSIS is the most common cause of posterior uveitis in the world, accounting for over 80% of cases in some regions.¹ It is caused by the obligate intracellular protozoan *Toxoplasma gondii*. Recurrence of congenital toxoplasmosis is still the leading cause of *Toxoplasma* retinochoroiditis, but acquired ocular disease is more common than previously suspected.²⁻⁵ More than 82% of congenitally infected individuals not treated as infants will develop retinal lesions by the time they reach adolescence.⁶

Ocular toxoplasmosis is usually a recurrent disease, and two thirds of patients present with relapses.⁷ We believe that recurrence is the result of release of *Toxoplasma gondii* trophozoites from cysts, which then actively infect the retina and release antigens stimulating an inflammatory retinochoroiditis. Some recurrences may actually be secondary to reinfection.

In this article we report four patients who had recurrences of ocular toxoplasmosis during their pregnancies, suffered from visual loss and had treatment-resistant inflammation.

METHODOLOGY

We reviewed 1,243 charts of patients followed in the Uveitis Service at the Massachusetts Eye and Ear Infirmary from November 1986 to December 2003. One hundred ninety seven patients had a diagnosis of ocular toxoplasmosis, and 4 of these patients were pregnant at the time of recurrence of their ocular disease. Clinical records of these patients were reviewed for details of clinical presentation, ophthalmic history, complications and visual outcome at final follow-up.

CASE REPORTS

Case 1

A 22 year-old Hispanic woman, an immigrant from El Salvador, presented to the Ocular Immunology and Uveitis Service of the Massachusetts Eye and Ear Infirmary with complaints of a decreased visual acuity and redness in her right eye of five days duration. The patient had an episode of intense pain in the right eye two weeks prior to the visit. The pain persisted for one week. At the time of examination the patient was 28 weeks pregnant. She was taking prenatal vitamins and did not have any allergies. Her medical history was unremarkable.

The patient's visual acuity was 20/50 (6/15) in the right eye and 20/20 (6/6) in the left eye. There were keratic precipitates on the corneal endothelium, and 3+ cells in the anterior chamber of the right eye. Dilated examination of the fundus revealed 3+ cells in the vitreous and an active focus of macula-threatening retinochoroiditis along the superotemporal arcade, and an old scar in the nasal periphery consistent with toxoplasmic lesions.

After consulting with the patient's gynecologist, the patient was begun on clindamycin 300 mg orally three times a day and atovaquone 750 mg orally twice a day. On the follow-up visit, the patient's visual acuity in the affected eye had decreased to 20/300 (6/90). The amount of cells in the anterior chamber increased to 4+ and vitreous cells were 2+. Systemic prednisone 50 mg orally daily and topical prednisolone acetate, one drop every hour in the right eye, were started. In spite of this therapy, inflammation persisted for the next three months. The patient developed posterior vitreous detachment after two months of therapy during her 33rd week of pregnancy.

Two weeks after giving birth, the patient returned for a follow-up visit. Examination revealed decreased vitreal cells to 1+ and mostly scarred toxoplasmic lesion. Visual acuity was 20/40 (6/12). Medications were discontinued.

Six weeks after delivery the patient's visual acuity was 20/25 (6/7.5) in the affected eye and there was no active inflammation. The child was healthy.

During her two-year follow-up the patient did not have recurrences of toxoplasmic retinochoroiditis.

Case 2

A 24 year-old Hispanic female with a history of panuveitis in both eyes for four years, treated with periocular steroids with little success, was referred for evaluation. The patient's medical history was remarkable for 2 caesarean deliveries. The patient reported a history of recurrence of toxoplasmosis with her second pregnancy, but this did not affect the birth of a healthy child.

At the time of the visit with us the patient's visual acuity was 20/30 (6/9) in the right eye and 20/70 (6/21) in the left eye. She was receiving one drop of prednisolone acetate hourly in the left eye. Slit-lamp examination showed posterior subcapsular cataract. Dilated fundoscopic examination revealed posterior vitreous detachment, 3+ old vitreous debris and 1+ cells in the left eye. There were bilateral choroidal lesions. Fluorescein angiography disclosed optic-disc staining of the left eye in the late frames.

The patient had undergone an evaluation, which disclosed an antitoxoplasmic IgG antibody level of 2.2 EIA units (normal range 0-0.9). Chest X-ray, gallium scan, and other laboratory tests were normal.

Because there were no vision-threatening lesions, we decided to observe the patient. Prednisolone acetate was slowly tapered. On subsequent visits the patient was found to have a progression of the cataract in her left eye and she scheduled phacoemulsification of the cataract combined with pars plana vitrectomy. Three weeks after the procedure, the patient developed a retinal detachment in the left eye and reactivation of uveitis. In that visit the patient also informed her care providers that she was 5 weeks

pregnant. The patient was referred for surgical treatment of the retinal detachment. The patient continued to have persistent inflammation in the left eye. Her condition finally stabilized with visual acuity of 20/50 (6/15) in the left eye by the third trimester of her pregnancy. The patient had a healthy baby and no reactivation of toxoplasmosis after the delivery.

Case 3

A 20 year-old Hispanic female from Brazil with a history of ocular toxoplasmosis diagnosed at 13 years of age was referred for treatment of decreased visual acuity of her right eye and pain of one-week duration. The patient was 8 weeks pregnant at the time of her initial evaluation at the Ocular Immunology and Uveitis Service. The patient

Table 1. Profile of 4 cases with recurrent ocular toxoplasmosis in pregnancy.

	Case 1	Case 2	Case 3	Case 4
Age	22	24	20	26
Affected eye	OD	OS	OD	OS
Visual acuity prior to flare-ups	20/25 (6/7.5)	20/40 (6/12)	20/50 (6/15)	20/100 (6/30)
Weeks of pregnancy at the beginning of flare-ups	28	2	7	19
Adverse events during flare-ups	Posterior vitreous detachment	Retinal detachment, cataract	Cataract	Progression of the disease to macula
Total length of inflammation	16 weeks	24 weeks	35 weeks	9 weeks
Worst visual acuity during flare-ups	20/300 (6/90)	20/200 (6/60)	Light perception with correct light projection	20/600 (2/60)
Final visual outcome	20/25 (6/7.5)	20/50 (6/15)	20/50 (6/15)	20/80 (6/24)
History of flare-ups with previous pregnancies	No previous pregnancies	Two previous pregnancies	Two previous pregnancies	One previous pregnancy

Table 2. Medications used in the treatment of ocular toxoplasmosis.

Medication	Typical dose	Safety in pregnancy
<i>Dihydrofolate reductase inhibitors</i> Pyrimethamine Trimethoprim/sulfamethoxazole ¹	100 mg loading dose 25-50 mg daily for 30-60 days 160mg/800 mg twice daily	Category C* contraindicated in the first trimester; excreted in human milk
<i>Sulfonamides</i> Sulfadiazine Sulfasoxazole Sulfadiazine/sulfamerazine/sulfamethazine ("triple sulfa") Trimethoprim/sulfamethoxazole ¹	1gm four times daily _____ _____ 160 mg/800 mg twice daily	Category C* contraindicated in third trimester and breastfeeding
<i>Tetracyclines</i> Minocycline	100 mg twice daily	Category D* contraindicated in pregnancy and childhood
<i>Prednisone</i>	1 gm/kg/day	Category C*
<i>Macrolides</i> Spiramycin Azithromycin	500 mg three times daily for 3 weeks. May repeat after 21 days 500 mg daily for 3 weeks	Category B*
<i>Antiprotozoal</i> Atovaquone	750 mg four times daily for 4-6 weeks	Category B*
<i>Lincomycin derivative</i> Clindamycin	300 mg four times daily for 30-40 days	Category B*
<i>Folinic acid</i>	5-20 mg every day during pyrimethamine therapy	Category A*

* Grading system of medications in pregnancy: **A** = safety established in human studies, **B** = presumed safety based on animal studies, **C** = uncertain safety—no human or animal studies; **D** = unsafe—evidence of risk that may be justifiable in certain clinical circumstances; **E** = highly unsafe—risk outweighs any possible benefit.

¹Trimethoprim/sulfamethoxazole is a combination of a dihydrofolate reductase inhibitor and a sulfonamide.

did not have any significant medical history or allergies, and was not taking any systemic medications. She was using topical prednisolone acetate hourly and scopolamine twice daily in her right eye. Her visual acuity was 20/400 (3/60) in the right eye and 20/20 (6/6) in the left eye. Slit-lamp examination revealed keratic precipitates on the corneal endothelium, 3+ cells in the anterior chamber, and pigment deposits on the anterior capsule of the lens of the right eye. Dilated fundus examination showed an active toxoplasmic lesion adjacent to an old scar in the right eye, and 3+ vitreous cells. The left eye had an old chorioretinal scar, but there were no signs of active inflammation.

The patient was begun on atovaquone 750 mg orally twice daily and clindamycin 300 mg orally four times daily. Her follow-up visit in 10 days revealed worsening visual acuity in the affected eye: light perception with correct light projection, 3+ cells in anterior chamber and increased vitreous cells (4+). Systemic prednisone was added to the regimen at a dose of 60 mg orally daily. In spite of this therapy, inflammation persisted for the remaining 7 months of the patient's pregnancy.

On her follow-up visit 3 weeks post-delivery the patient's visual acuity remained at 20/400 (3/60). There was active inflammation with 3+ cells in the anterior chamber and extensive posterior synechiae obstructing the view of the fundus, along with posterior subcapsular cataract. Atovaquone was substituted with pyrimethamine 25 mg orally twice daily, folic acid 5 mg orally twice weekly and sulfadiazine 1000 mg four times daily. The patient was continued on clindamycin. Control of inflammation was achieved within five weeks after delivery, with resulting visual acuity of 20/80 (6/24) in the right eye.

Case 4

A 26-year-old Hispanic female with a history of ocular toxoplasmosis and glaucoma was referred for further evaluation and treatment. The patient was 22 weeks pregnant with her second child. She reported a history of recurrence of toxoplasmosis during her first pregnancy, leaving her with vision of 20/100 (6/30) in the left eye. The patient complained of loss of vision in her left eye for three weeks. She was started on therapy by the physician who saw her at that time. She was taking clindamycin 300 mg orally four times daily, sulfadiazine 500 mg orally twice daily, timolol maleate (Timoptic 0.5%, Merck Sharpe & Dohme, PA, USA) 1 drop and brimonidine (Alphagan Allergan, CA, USA) 1 drop twice a day in the left eye, as well as prednisolone acetate 1 drop four times daily in the left eye. Visual acuity was 20/25 (6/7.5) in the right eye and 20/600 in the left eye. Intraocular pressure was 15 mm Hg in the right and 21 mm Hg in the left eye. Slit-lamp examination showed 2+ cells in the anterior chamber of the left eye. The dilated fundus examination was

significant for an active inflammatory lesion in the macula and 2+ vitreal cells. Cup-to-disc ratio was 0.5 in the right and 0.6 in the left.

An infectious disease specialist recommended increasing the dose of clindamycin to 450 mg orally four times daily, and increasing sulfadiazine to 1 g orally four times daily. Three weeks later the patient returned with resolution of the anterior chamber inflammation, but 2+ vitreous cells persisted. Control of inflammation was achieved in three more weeks of continued therapy. Visual acuity in the left eye remained 20/800 (1.5/60).

RESULTS

We have described four patients with recurrent ocular toxoplasmosis during their pregnancy. The clinical features are summarized in Table 1.

Two patients had recurrence of toxoplasmic retinochoroiditis early in pregnancy, at 2 and 7 weeks, and the other two patients had recurrences at 28 and 19 weeks of pregnancy. All participants had a violent course of inflammation. Three patients had a prolonged course. Three of the four patients had permanent decrease in their best corrected visual acuity. Two developed cataracts and one developed retinal detachment. One patient had a decrease in visual acuity from 20/100 (6/30) to 20/800 (1.5/60) in the affected eye due to macular involvement in spite of aggressive therapy and a short duration of inflammation. Interestingly, two participants provided history of recurrences of ocular toxoplasmosis during their previous pregnancies. The details were unavailable for those incidents. Natural termination of pregnancy appeared to help the resolution of inflammation in two patients.

DISCUSSION

Many women are diagnosed with or experience recurrence of ocular toxoplasmosis during pregnancy. Newly diagnosed ocular toxoplasmosis in pregnant women is much less common than recurrence of toxoplasma retinochoroiditis. Pregnancy creates an interesting immunologic state in which strong immune responses are suppressed in order to prevent rejection of a fetus by the mother, and pregnancy-associated immunomodulation is thought to cause an ameliorating effect on some of the autoimmune diseases, such as multiple sclerosis,⁸⁻¹¹ rheumatoid arthritis,^{12,13} juvenile idiopathic arthritis¹⁴ and sarcoidosis¹⁵. The effect of pregnancy on the eye has not been studied well. Pregnancy associated immunomodulation may have a deleterious effect in patients with infectious ocular disorders.

It is well known that immunocompromised patients are at increased risk for developing acute toxoplasmosis, which has a poor prognosis and may be rapidly fatal if left untreated. Ocular toxoplasmosis may follow a severe

course in patients with AIDS, having atypical features, such as large areas of retinal necrosis,¹⁶ lesions arising perivascularly and not from old scars,¹⁷ bilateral inflammation, and inflammation extending into the orbit and causing cellulitis and panophthalmitis.¹⁸ Ocular toxoplasmosis may be more severe in elderly patients due to age-related waning of host immune defenses.^{19,20}

Certain timidity exists, even in specialty-trained uveitis specialists when treating pregnant patients with ocular toxoplasmosis. In one survey the majority of physicians stated that they would treat only severe vision-threatening acute toxoplasmosis in pregnant women.²¹ Adverse effects which medications may cause to the fetus limit treatment options for pregnant women with toxoplasmic retinochoroiditis.

In Table 2 we review the safety of medications used in treatment of ocular toxoplasmosis.

Combination clindamycin and atovaquone may provide a safe approach to treatment of acute ocular toxoplasmosis in pregnant patients. The optimal duration of specific therapy must be adjusted according to therapeutic response. We define a positive response to treatment as a sharpening of the borders of retinochoroidal lesions and decrease of vitreal cells. We continue therapy in immunocompetent patients at least for 30-60 days. Addition of oral corticosteroids may be started within 48 hours after initiation of antimicrobial therapy for intense ($\geq 3+$) vitreal cellular response.

A macrolide, such as clindamycin or azithromycin, combined with atovaquone may provide an excellent treatment option for pregnant patients. Sulfonamides should be avoided in the third trimester, because they compete with bilirubin for serum proteins, causing kernicterus. Pyrimethamine is potentially teratogenic and should be avoided, especially in the first trimester.

Comanagement with an infectious disease specialist is advised, as is consultation with an obstetrician. Some agree that there is a lack of evidence to support routine employment of antibiotic treatment for acute toxoplasmic retinochoroiditis in the general population.²² But it may be especially important to treat medically pregnant women with ocular toxoplasmosis, since antibiotic therapy prescribed to mothers who have toxoplasmic retinochoroiditis during pregnancy decreases the percentage of children developing retinochoroidal toxoplasmic lesions during the first and second years of life.^{23, 24, 25, 26}

Pars plana vitrectomy may be useful in the care of selected patients with toxoplasma retinochoroiditis for removal of antigenic proteins, inflammatory cells, and persistent vitreous opacities. Intravitreal/intraocular antibiotic injections may be an option for treating pregnant patients with ocular toxoplasmosis,²⁷ thereby avoiding systemic toxicity, side effects, and possible

teratogenicity. Martinez and colleagues²⁷ reported a case series of pregnant women with active toxoplasmic retinochoroiditis, who were treated with a combination of intraocular clindamycin and dexamethasone with good visual outcomes. We have successfully treated several cases of ocular toxoplasmosis unresponsive to conventional therapy with intravitreal injections of clindamycin.²⁸ Patients in our series were not pregnant. They had intolerance to systemic therapy. The resolution of inflammation in these patients and improvement in visual acuity make us believe that penetration of systemic medications may be inadequate in treatment of ocular toxoplasmosis and is responsible for the poor visual outcomes in the pregnant women described in this article.

The host immune system plays a critical role in response to ocular toxoplasmosis. It has been postulated that pregnancy may be a triggering factor in the recurrence of ocular toxoplasmosis.^{29,31} Friedman and Knox³⁰ reported active toxoplasmic retinochoroiditis during five pregnancies of four patients, and Bosch-Driessen et al.³¹ described seven women with ocular toxoplasmosis who had recurrences during pregnancy. Four of those women had reactivation of toxoplasmic lesions with each subsequent pregnancy. We believe that pregnancy not only predisposes a patient for recurrence of ocular toxoplasmosis, but may also present favorable conditions for a more aggressive form of this disease. Large cohort studies may lead to a better understanding of toxoplasmosis in pregnancy.

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CASE REPORT

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Manifestations of Bardet-Biedl syndrome

ABSTRACT

Objective

To report the first documented case of Bardet-Biedl syndrome at the University of the Philippines Philippine General Hospital.

Methods

This is a case report.

Results

A 7-year-old boy was diagnosed to have Bardet-Biedl syndrome based on the presence of five of the six primary manifestations of the disease: retinitis pigmentosa, obesity, postaxial polydactyly, learning disabilities, hypogenitalism, and renal dysfunction.

Conclusion

Bardet-Biedl has ocular and systemic manifestations requiring a multi-disciplinary approach to treatment.

Keywords: *Bardet-Biedl syndrome, Retinitis pigmentosa, Polydactyly, Hypogenitalism*

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BARDET-BIEDL syndrome (BBS) is an autosomal recessive condition characterized by rod-cone dystrophy, postaxial polydactyly, central obesity, mental retardation, hypogonadism, and renal dysfunction. Other features, though not always present, are hepatic fibrosis, diabetes mellitus, reproductive abnormalities, endocrine abnormalities, short stature, developmental delay, and speech deficits.¹

BBS is genetically heterogenous with at least 6 loci mapped to date. The most common gene is BBS1 located at chromosome 11.² Other genes identified are BBS2 at chromosome 16, BBS3 at chromosome 3, BBS4 at chromosome 15, BBS5 at chromosome 2, and BBS6 at chromosome 20.³

The syndrome is relatively rare. It is estimated to be 1 in 160,000 in Switzerland. It is more common among Arab populations, specifically the Bedouins of Kuwait,⁴ where interfamilial marriages are common. In Newfoundland, Canada, the incidence is 1 in 17,500. In the Philippines, no case has been reported yet.

In this article we describe a case of Bardet-Biedl Syndrome presenting the features seen in the patient.

CASE HISTORY

A 7-year-old boy presented with a history of blurring of vision of two years duration, developmental delay, and nightblindness. Weighing 5.8 pounds at birth, he was born full term via spontaneous vaginal delivery to a 28-year-old primigravida, who was on rifampicin for pulmonary tuberculosis during the first 3 months of pregnancy. The patient was noted to have six digits on all extremities and a small penis. At 3 months of age, he was treated with rifampicin for primary complex.

The eldest of 2 children (the sibling is normal), he was noted to have developmental delay upon consultation, with a developmental age equivalent to a 3- to 4-year-old. Best-corrected visual acuity was 20/70 (6/21) on the right eye and 20/50 (6/15) on the left. Refraction was plano \approx -4.00 cyl at axis 180 for both eyes. External adnexae were normal. Pupils were 3 mm and briskly reactive to light with no afferent pupillary defect (APD). The patient was orthophoric with a full range of ocular movements. Intraocular pressures were normal. Biomicroscopic examination revealed normal anterior segment.

Indirect ophthalmoscopy revealed attenuated retinal vessels, atrophic retinal pigment epithelial (RPE) changes (Figure 1), and sparse pigmentation at the retinal periphery.

Electroretinogram (ERG) showed findings consistent with tapetoretinal degeneration and retinitis pigmentosa (Figure 2). Visual-field examination was unreliable.

Physical examination showed the patient was obese and had hexadactyly (Figure 3) and micropenis (Figure

4) measuring approximately 2 centimeters in length, with descended testes and a labia-like scrotum. The patient also had small dental roots and hypodontia (Figure 5).

DISCUSSION

Differential diagnoses

Based on the ocular findings and systemic manifestations, the following differential diagnoses were considered: Weiss syndrome, Biemond II syndrome, Laurence Moon syndrome, Alstrom syndrome and Bardet-Biedl syndrome.

Alstrom syndrome is characterized by tapetoretinal degeneration, obesity, preaxial polydactyly, diabetes mellitus, and neurogenic deafness.⁵ The patient had only two (obesity, polydactyly) of these manifestations. His blood glucose was normal and he had no symptoms of diabetes. Neither did he have neurogenic deafness. The other findings seen in this patient (hypogonadism, post axial polydactyly, and learning disability) are not manifestations of Alstrom syndrome.

Biemond II syndrome is characterized by ocular defects (more specifically iris coloboma), learning disability, polydactyly, obesity, and hypogonadism.⁶ Although the patient had four of the main characteristics, retinal dystrophy is not a characteristic of this syndrome.

Obesity, mental deficits, genital dystrophy, nerve deafness, and short stature characterize Weiss syndrome,⁶ which were all seen in the patient. But the patient had retinal dystrophy, which is not characteristic of this syndrome.

Laurence Moon syndrome is characterized by retinitis pigmentosa or rod cone dystrophy, mental deficiency, hypogonadism, and spastic paraparesis.⁶ The patient, however, had no spastic paraparesis and patients with Laurence Moon syndrome do not show polydactyly and obesity.

Similar to Laurence Moon syndrome, Bardet-Biedl syndrome is characterized by retinitis pigmentosa, obesity, postaxial polydactyly, learning disabilities, hypogonadism, and in some cases, renal dysfunction.⁶ With 5 of the 6 characteristics present in this patient, he was diagnosed to have Bardet-Biedl syndrome.

Diagnostic criteria for Bardet-Biedl syndrome

Beales et al. developed the diagnostic criteria for Bardet-Biedl syndrome: the presence of four primary features or a combination of three primary features plus two secondary features.¹

The primary features are rod-cone dystrophy, polydactyly, obesity, learning disabilities, hypogonadism in males, and renal anomalies. The patient met 5 of these criteria.

Secondary features are speech disorder/delay, strabismus, cataracts, astigmatism, syndactyly, brachydactyly,

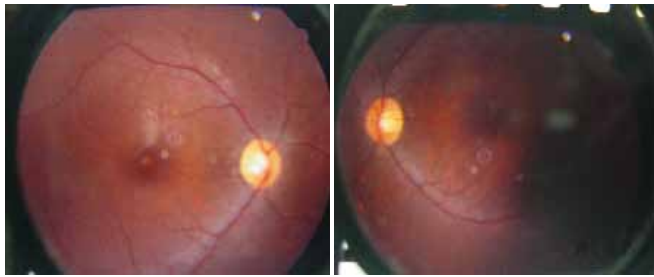


Figure 1. Fundus photos showing attenuation of retinal vessels and scattered RPE changes.

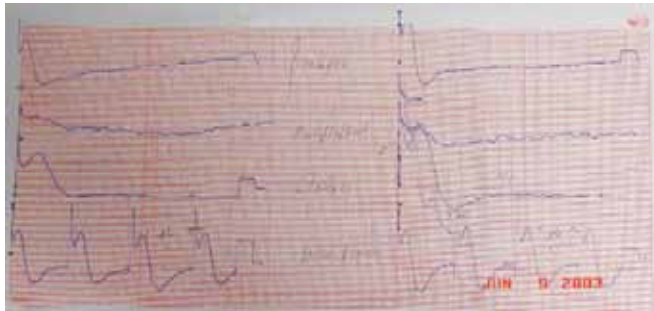


Figure 2. ERG tracing.



Figure 3. Hexadactyly.

developmental delay, polyuria and polydipsia. The patient had astigmatism, speech disorder, developmental delay, and brachydactyly (Figure 6).

Additional secondary features are hypodontia/small tooth roots, dental crowding, high arched palate, mild spasticity, diabetes mellitus, left ventricular hypertrophy/congenital heart disease, hepatic fibrosis, ataxia, poor coordination, and imbalance. The patient had hypodontia and small tooth roots.

On the average, Bardet-Biedl syndrome is diagnosed at 9 years of age. The relatively late age of diagnosis can be explained by the slow development of clinical features. The first visual disturbance is usually night blindness.

Retinopathy

Retinitis pigmentosa is a disease characterized by progressive photoreceptor degeneration with RPE atrophy and intraretinal pigment migration of the RPE.⁷ Symptoms include progressive contraction of the visual fields and night blindness. Decreased visual acuity can result from macular involvement of the disease.



Figure 4. Micropenis.



Figure 5. Hypodontia.



Figure 6. Brachydactyly.

Attenuated vessels, mottling, granularity of the RPE, bone spicule formation, and waxy pale appearance of the disc are typical fundus findings in retinitis pigmentosa. Rod-cone dystrophy found in Bardet-Biedl syndrome is an atypical form of retinitis pigmentosa characterized by early decrease in visual acuity related to early macular involvement. The retinal periphery often has sparse bone spicule pigmentation, with central and peripheral RPE

atrophy. Vessel attenuation and disc pallor are also present.⁸ The retinal findings in this patient were consistent with an atypical presentation.

Other findings were constricted visual fields, severe color deficiency, raised dark-adapted thresholds, extinguished and minimal rod and cone responses on ERG. Visual-field testing and color testing were unreliable because the patient was uncooperative. The ERG showed findings consistent with retinitis pigmentosa.

Learning disabilities

Sixty-two percent of Bardet-Biedl syndrome patients have learning disabilities and short-term memory deficit, which is often counterbalanced by excellent long-term memory. These patients perform much better at performance rather than verbal skills.¹ A recent study in the United Kingdom showed that the majority of children with Bardet-Biedl syndrome were able to remain in mainstream education in the early years. In time, however, almost half required placement in special schools.

Obesity

Obesity is a major problem in this syndrome and is one of the most frequent reasons for medical consultation. It is present in 75% of patients. Excess weight gain does not usually begin until 1-2 years of age. The cause is unknown but the mechanism of obesity appears to be a complex combination of hyperphagia and altered disposal of calories.¹

Postaxial polydactyly

The presence of extra digits is a distinct feature of Bardet-Biedl syndrome where 66% of patients have postaxial hexadactyly ranging from a single skin tag to a fully formed digit on all four limbs. Brachydactyly—having short stubby fingers and toes—is common. When present, it can considerably affect dexterity. Syndactyly is less frequently seen but is usually partial and confined to the feet.¹

Hypogenitalism

Hypogenitalism occurs mostly in men; 88% were found to have small testes and very small penises. These patients, however, have normal testosterone levels. Women with Bardet-Biedl syndrome usually have normal secondary characteristics but often have menstrual irregularities and endocrine dysfunction with increased luteinizing hormone.⁹ This patient had a penis about 2 centimeters in length.

Renal dysfunction

Renal abnormalities can lead to life-threatening problems. Some patients have structural abnormalities in

the form of dysplastic kidneys with irregular contour and cystic dilatation of collecting ducts and calyces. About 15% develop symptomatic renal impairment, with 5% going into end-stage renal failure.¹⁰ This patient had normal kidneys on ultrasonography and normal parameters of renal function. Intravenous pyelography may be a useful test in some patients.

Secondary features

The secondary features present in this patient were astigmatism, brachydactyly or short stubby feet, developmental delay, speech disorders and dental problems. This patient did not manifest any cardiac, hepatic or endocrine abnormalities.

Management

Bardet-Biedl syndrome is recessively inherited with both parents being phenotypically normal. The risk of subsequent offspring being affected is 25%. There is a two-thirds chance that unaffected siblings will be carriers. When a new case is seen, a careful family history should be taken and other relatives examined. In this case, the patient was the only one affected in his family.

Beales and coauthors recommend that all patients suspected of Bardet-Biedl syndrome undergo baseline ERG, renal ultrasound, intravenous pyelography, ECG, and echocardiogram.¹ Follow-up include biannual urinalysis and annual blood pressure, serum urea, and creatinine screening to monitor for development of renal dysfunction.

Much can be done to address the ophthalmologic problems of patients with Bardet-Biedl syndrome. Careful refraction should be performed for visual rehabilitation. The patient should also be prepared for a life with low vision. For retinitis pigmentosa, Vitamin A has been found effective in slowing down the decline in ERG responses.⁷ However, these findings were based on patients with typical retinitis pigmentosa and not syndromic retinitis pigmentosa.

Although ocular manifestations may be the most significant aspect of the disease, other systemic problems should be addressed. Treatment of Bardet-Biedl syndrome is directed toward specific organs and systems. A multidisciplinary approach is suggested with the ophthalmologist addressing the problems of retinitis pigmentosa (RP) and visual rehabilitation.

The pediatrician should be involved in the overall care of the patient and refer the patient to appropriate subspecialties when necessary.

Intervention for renal dysfunction depends on the type of abnormality seen. Recurrent infections due to reflux are treated with appropriate antibiotics. If structural changes have been identified then twice-yearly urinalysis

and work-up for functional abnormality should be done. A few patients would require dialysis or even renal transplant.

Testosterone supplements have not been beneficial for patients with genital abnormalities.¹¹ Puberty is a particularly stressful time for these patients and counseling can be of immense help.

Control of diabetes can prevent diabetic retinopathy and rapid deterioration of vision already compromised by rod-cone dystrophy. A cardiologist should be consulted for suspected cardiovascular problem.

An orthopedic surgeon may be consulted for possible excision of excess digits to help the patient maximize function. Specially fitted shoes are beneficial to patients with bone deformation.

A dietician or nutritionist should be engaged in addressing obesity, which is a major source of stress for both patient and parents. Given the complex etiology of weight gain in Bardet-Biedl, a multidisciplinary approach is recommended in dealing with weight loss. This may include a combination of careful dietary assessment, diet, behavioral therapy, and exercise.

Learning difficulties should be addressed early, before visual impairment interferes, if possible. Special schools

can aid in providing a program for these patients.

We have described a patient with Bardet-Biedl syndrome and is the first reported case at the Philippine General Hospital.

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COMMENTARY

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The implications of randomized, controlled clinical trials in glaucoma on clinical practice

What does the evidence tell us?

SUMMARY

Lowering intraocular pressure (IOP) to prevent disease progression in open-angle glaucoma has been an accepted practice for more than a century. However, strong clinical evidence on the beneficial effect of IOP reduction has only become available in the past few years with such studies as the Ocular Hypertension Treatment Study (OHTS), the Early Manifest Glaucoma Trial (EMGT), the Collaborative Initial Glaucoma Treatment Study (CIGTS), and the Advanced Glaucoma Intervention Study (AGIS). This article dissects each of these studies and extracts points that are relevant to clinical practice.

The OHTS study showed that not all patients with ocular hypertension need to be treated. The magnitude of IOP elevation and the presence of other risk factors should be considered before initiation of treatment. Ocular hypotensive treatment in the high-risk subset of patients will delay or prevent the development of glaucoma. Moreover, it revealed that central corneal thickness may confound Goldmann applanation tonometry measurements.

The EMGT is the first adequately powered randomized controlled clinical trial to demonstrate the beneficial effect of lowering the IOP in open-angle glaucoma (OAG) patients. It showed a positive correlation between the level of IOP reduction and the risk of progression.

The CIGTS showed the importance of aggressive therapy (medical, laser and/or surgical) and setting individualized IOP target based on the patient's glaucoma status and baseline IOP. It expounded on the concept of quality of life as a measure of success in the treatment of glaucoma.

The AGIS trial showed that lowering IOP to below the upper limit of statistically "normal" levels (e.g. <21 mm Hg) may not be enough to prevent progression in patients with OAG. Patients who had sustained greater IOP reduction had a more favorable outcome in terms of visual-field preservation.

All these trials confirmed the beneficial effect of IOP reduction in OAG. They showed that the management of glaucoma patients must be individualized to help preserve vision and maintain quality of life. Caution should be used when interpreting the data in these studies. The applicability of recommendations to our patients should be ascertained by looking at the characteristics of the patients in each of these studies. Limitations in the local setting, the availability of resources, patient preferences, and our expertise in the clinical decision-making process should be considered.

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The Ocular Hypertension Treatment Study (OHTS)^{1, 2}

Reviewed by Jose Ma. G. Martinez, MD

STUDY SUMMARY

A randomized clinical trial involving 22 clinical centers in the United States of America, the OHTS aimed to determine the safety and efficacy of topical hypotensive medication in delaying or preventing primary open-angle glaucoma (POAG) among ocular hypertensives. It also sought to identify predictive baseline factors for the development of POAG. The study population was mostly Caucasian (70%) and African American (25%); aged 40 to 80 years; IOP between 24 mm Hg and 32 mm Hg; and normal optic discs and visual fields. Randomized into treatment and control groups were 1636 participants. Target IOP reduction for the treatment group was 20% using a topical hypotensive agent.

The patients were followed up at regular intervals, with periodic visual-field testing and optic-nerve-head stereophotography for 5 years. The development of glaucomatous nerve damage and visual-field defects as evaluated by an independent masked committee using standard criteria were considered primary outcome measures.

During the course of the study, the mean IOP reduction was 22% in the treatment group and 4% in the observation group. The cumulative probability of developing POAG after 60 months was 4.4% in the medication group and 9.5% in the observation group (Hazard Ratio (HR)= 0.40; 95% CI, 0.27-0.59; $p < .0001$) a 46% reduction of risk. In multivariate analyses, the significant baseline predictive factors for POAG were thin central cornea (HR=1.71 per 40 micron disease), larger vertical cup-to-disc ratio (HR=1.32), higher pattern standard deviation (PSD) on standard achromatic perimetry (HR=1.27), and advanced age (HR=1.22). There was no significant difference ($p > 0.05$) in the rate of serious adverse events between the two groups. The authors concluded that topical hypotensive medication effectively delays or prevents the onset of POAG among ocular hypertensives.

COMMENTS

To date, the OHTS study has the largest sample size among all studies involving ocular hypertension. Eligibility criteria as well as end-point criteria were well defined using the most acceptable methods of stereophotography and automated achromatic perimetry. Although the subjects and clinicians were not masked, masked evaluators (glaucoma specialists) analyzed the main outcome measures. Patients in both groups had similar

rates of dropouts, nonadherence to randomization, and subjects who completed the study. Patients were analyzed according to their randomization groups.

The study had several sources of selection bias. The subjects were generally healthy; few had debilitating systemic diseases. As a result, diabetes mellitus, shown to be a significant predisposing factor for glaucoma in other studies, was protective for the disease on multivariate analysis. The study was also selective of subjects who could do reliable perimetry and who had clear media for optic disc photography. The range of IOP studied was between 21 and 32 mm Hg. The study results can not provide quantitative data pertaining to patients outside of this IOP range. The risk of glaucoma damage increases exponentially (not linearly) with higher IOP above 30 mm Hg.³ Thus, data in this study cannot be applied to patients with pressures above 32 mm Hg.

IMPLICATIONS ON CLINICAL PRACTICE

It is tempting to treat all ocular hypertensives given the large reduction of risk—50%. It is also easy to convince patients to take the side of “preventive” treatment with this figure. One only has to look at the whole picture to see that less than 15 % of patients in the study eventually developed glaucoma. The rarity of conversion to frank POAG is in keeping with other studies by Linner (34%, $n=41$)⁴ and Armaly (1.7%, $n=5886$).⁵ With a low event rate and little functional disability from the “disease” at its early stages, it is prudent to exercise caution in choosing whom to treat. The number needed to treat is 20 to prevent 1 patient from developing glaucoma. Treatment for all ocular hypertensives then becomes simply too costly for the benefit gained.

Most of the positive risk factors like age, larger CD ratio, and higher PSD are well known and have been validated by this study. Optic nerve head changes typically appear earlier than visual-field defects, and as such, close monitoring requires good optic-nerve evaluation.

The inclusion of CCT was the most interesting feature of the study. This represented a new, measurable factor that can strongly predict the development of POAG. Clinicians should definitely screen patients for thin corneas by doing pachymetry on all ocular hypertensives. As central corneal thickness obviously exerts its influence through errors in applanation measurements, doing pachymetry in all glaucoma patients may be justified.

The ultimate consideration, especially in economically challenged situations, is weighing costs against benefits. Costly treatment should be reserved for those who are sure to have the disease. Diligent follow-up becomes the key in managing ocular hypertension. This study shows clinicians how to conduct this follow-up and what to look for in each individual patient.

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Early Manifest Glaucoma Trial (EMGT)^{1,2}

Reviewed by Patricia M. Khu, MD, MS

STUDY SUMMARY

Enrolled were 255 patients aged 50 to 80 years (median, 68 years) with early glaucoma defined as follows:

- Newly detected, previously untreated primary open-angle glaucoma, normal-tension glaucoma, or exfoliation glaucoma;
- Reproducible glaucomatous visual-field defects (Humphrey 24-2 full threshold) in at least one eye.
- Mean deviation (MD) ≤ 10 dB in at least one eye and no threat to fixation ≥ 10 dB at test points closest to point of fixation);
- Visual acuity ≥ 0.5 (20/40 or 6/12) in any eye;
- Mean IOP ≤ 30 mm Hg and no IOP > 35 mm Hg in any eye.

Eligible patients were randomized evenly as control (n=126) and treatment (n=129) groups. All eyes randomized to treatment received a full 360° trabeculoplasty plus betaxolol 0.5% (Betoptic 0.5%, Alcon, Forth Worth, TX, USA) twice daily. Study visits included visual-field tests and tonometry every 3 months, and optic-disc photography every 6 months. Latanoprost 0.005% (Xalatan, Pfizer, NY, NY, USA) once daily was added if IOP after 2 consecutive follow-ups exceeded 25mm Hg in the treatment group and 35mm Hg in the control group.

Patients stayed in their allocation arms unless significant progression occurred, defined as either of the following:

- Visual-field progression: 3 or more test-point locations showing significant deterioration from baseline in glaucoma change probability maps from 3 consecutive tests;
- Optic-disc progression: determined by masked graders using flicker chronoscopy plus side-by-side photogradings.

After a median follow-up period of 6 years, treatment reduced the IOP by 5.1 mm Hg or 25%, which was maintained throughout follow-up. Progression happened less

frequently in the treatment group (58/129; 45%) than in the control (78/126; 62%) ($p = 0.007$) and occurred significantly later in treated patients (66 months v. 48 months in control). Progression varied across patient categories, but treatment effects were present in both older and younger patients, high- and normal-tension glaucoma, and eyes with less and greater visual-field loss. These effects were greater with longer follow-up.

In multivariate analyses using median values, treatment halved the risk for progression (HR=0.50; 95% CI, 0.35-0.71). Predictive baseline factors for progression were higher IOP (HR=1.70), exfoliation (HR=2.31), involvement of both eyes (HR=1.93), worse MD (HR=1.55), and older age (HR=1.43). Using continuous values, the risk of progression increased by 5% with each mm Hg of higher baseline IOP (HR=1.05; 95% CI, 1.01-1.10), by 3% per 1dB of worse MD (HR=1.03; 95% CI 0.98-1.09), and by 1% per 1 year of age (HR=1.01; 95% CI, 0.98-1.05). Progression risk decreased by about 10% with every mm Hg of IOP reduction from baseline to first follow-up visit (HR=0.90; 95% CI 0.86-0.94).

COMMENTS

The EMGT is a well-conducted randomized, controlled clinical trial evaluating the effectiveness of reducing IOP in patients with newly detected, previously untreated early glaucoma. It has a control arm in which patients underwent follow-up without treatment as long as progression did not occur. The two groups have the same number of participants, similar rates of follow-up, and low attrition rates (2.4%).

There was no selection bias; eligible patients were randomized evenly between the groups according to a permuted block randomization scheme stratified by the clinical and satellite centers. Data on both visual-field and optic-disc outcomes were obtained by masked observers. The visual-field criterion used was based on previously tested statistical programs for visual-field analysis and was numerical and objective. The glaucoma-change probability maps were based on pattern deviation rather than total deviation, strongly reducing any confounding effects of progressing lens opacities on visual-field outcomes.³ Moreover, the criterion for visual-field progression was defined at the start of the trial and was not changed during the study.

The EMGT perimetric criterion has high sensitivity and was able to detect visual-field changes earlier than other measures of progression.^{4,5} In this study, the progression of glaucoma was determined principally by using the visual-field criterion, either alone or with corresponding optic-disc findings. Only one patient in the treatment group had progression based solely on optic-disc changes. The inclusion of both criteria

independent of each other and the stringent manner by which progression was assessed made possible the detection of definite early glaucomatous changes, even in the absence of modern perimetric methods of assessing early functional changes (frequency doubling perimetry or short wavelength perimetry), or methods of quantifying morphologic changes in the optic-nerve head and retinal nerve-fiber layer (retinal tomography, scanning laser polarimetry or optical coherence tomography). The EMGT criteria for progression were applied equally to both groups by outcome assessors who were masked as to the treatment assignment of each patient. Even though the patients and the treating physicians were not masked, the study personnel measuring the visual acuity, IOP, and visual fields were masked to patients' study group. Hence, those obtaining study outcomes were unaware of the study grouping of each patient and the results recorded were therefore not biased.

To remove the effect of compliance to glaucoma medications, the standard treatment used in this study included laser trabeculoplasty (LTP) in addition to a glaucoma medication. This was to avoid fluctuating IOP over the period of observation. LTP provides temporary but good IOP reduction and can be used either to supplement glaucoma medications or as first-line treatment.⁶

Study limitations

The patients were recruited during a population screening and data obtained could only be extrapolated to the general population. Moreover, the study involved a specific, homogenous patient population of white individuals and may not be applicable to other ethnic groups whose glaucoma progression may be different. Patients in this study also had relatively early glaucoma with IOP no greater than 30 mm Hg and mild visual-field defects, so the study results cannot provide quantitative data pertaining to patients with IOP levels greater than 30 mm Hg, or to those with advanced visual-field loss. Once progression was determined in patients of either group, glaucoma medication was added. This shortened the ascertainment of the natural history of glaucoma.

The EMGT only studied the beneficial effects of IOP lowering and did not study other risk factors (non-IOP risk factors) that may play a role in glaucoma progression.

IMPLICATIONS ON CLINICAL PRACTICE

In the era of evidence-based medicine, the EMGT is the first randomized study providing a long-term comparison of progression between treated and untreated patients with early glaucoma. The results not only confirm previous beliefs that IOP reduction is beneficial but also

provide new knowledge on rates of disease progression, with and without treatment, in patients with various characteristics. The results also support the need for early detection and treatment of glaucoma to prevent blindness.

The time to progression varied greatly among treated and untreated patients in this study, indicating that there were different rates of progression for different patients and different responses to the same treatment regimen. In the treatment group, either there was inadequate IOP control in those who progressed or there were other risk factors present (non-IOP risk factors) that played a major role in the progression of the disease. This demonstrated that a standard treatment regimen was insufficient to prevent progression in all glaucoma cases, specifically in those where the disease process was more rapid. In the "no treatment" group, many also showed no progression after six or more years of follow-up. Thus, the treatment regimen should be individualized for each patient, taking into consideration the presence of different risk factors. Careful follow-up may allow deferment of treatment in some patients until the rate of disease in the particular individual has been established over a period of observation.

How relevant are the results of the EMGT study to our clinical practice? One way is to look at the measures of treatment effect as follows:

Progression	Control	Treatment
Baseline risk	61.9%	45.0%
Relative risk (RR)		0.73
Relative risk reduction (RRR)		0.27
Absolute risk reduction (ARR)		16.9%
Number needed to treat (NNT)		6

The baseline risk for progression in the "no treatment" group is approximately 62% and in the treatment group 45%. The relative risk (comparing treatment to control) is 73% and the relative risk reduction (opposite of RR) is 27%. The absolute risk reduction is almost 17%, obtained by subtracting baseline risk of treatment group from that of control group. Getting the inverse of ARR is the number needed to treat to see the immediate effect of treatment. The NNT is small if the baseline risk is high and large if the baseline risk is low. In this study, for every 6 patients undergoing glaucoma treatment, progression is prevented in one patient. This is highly significant since its beneficial effect is seen in treating just six patients. This clearly indicates that *every* patient with early glaucoma should undergo treatment to prevent progression of the disease.

The EMGT study also supports the contention that the lower the initial IOP reduction in early glaucoma, the lower the risk of progression. For every 1 mm Hg decrease in the IOP on follow-up, there is an approximate 10%

decrease in the risk of progression. Thus, the IOP achieved after the initial reduction is a major predictor of future progression.

In cases where patients do not comply with their glaucoma medications or do not report for follow-up regularly, maintaining a low IOP by whatever means can be beneficial in preventing glaucoma progression. Options for maintaining persistently low IOP include potent once-a-day glaucoma medications (prostaglandin analogues), addition of laser trabeculoplasty, or glaucoma filtering surgery. These options can be used to lower the IOP with minimal effect on the quality of life of the patients. An additional 1 mm Hg difference in IOP lowering may not be much in the short term, but may mean preservation of vision in the long term. Glaucoma is a lifelong disease and the 17% reduction in the risk for progression for many years may be enough to prevent blindness.

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Collaborative Interventional Glaucoma Treatment Study (CIGTS) Interim Results¹

Reviewed by Joseph Anthony J. Tumbocon, MD

STUDY SUMMARY

This is an ongoing randomized, controlled clinical trial designed to determine whether patients with newly diagnosed open-angle glaucoma are better treated initially with medication or immediately by filtration surgery (trabeculectomy with or without 5-fluorouracil).

Glaucomatous damage was defined by the presence of one of the following criteria:

- A qualifying intraocular pressure (IOP) of ≥ 20 mm Hg, with a Humphrey visual-field (HVF/standard achromatic perimetry) result that includes ≥ 3 contiguous points on the total deviation probability plot at the less than 2% level and a Glaucoma

Hemifield Test result that is “outside normal limits,” and optic discs compatible with glaucoma, or

- A qualifying IOP of 20 to 26 mm Hg, with a HVF result that includes ≥ 2 contiguous points in the same hemifield on the total deviation probability plot at the less than 2% level and glaucomatous optic-disc damage, or
- A qualifying IOP ≥ 27 mm Hg, with glaucomatous optic-disc damage (no required visual-field changes).

Six hundred seven (607) patients (mean age 57.5 years) from 14 clinical centers were enrolled from October 1993 to April 1997. Most were diagnosed to have primary open-angle glaucoma (90.6%). Pigmentary and pseudoexfoliation glaucoma accounted for 4.6% and 4.8% respectively. Adaptive randomization was performed. The patients were assigned to either initial medical therapy (n=307) or primary trabeculectomy \pm 5-fluorouracil (n=300). Visual-field scores^{1,5} were generated on the basis of a weighted summary of the deficits on the Humphrey total probability plot. The two groups had similar baseline characteristics: visual-field score, visual acuity (VA), IOP, cup-to-disc ratios, age, study site, gender, race, diagnosis, family history of glaucoma, presence of hypertension and diabetes mellitus.

The patients in both groups were aggressively treated to lower the IOP to a predetermined individualized target based on the patient’s baseline pretreatment IOP and visual-field score (Target IOP = $(1 - [\text{reference IOP} + \text{visual-field score}]/100) \times \text{reference IOP}$). In the surgical arm, the patient underwent trabeculectomy within 14 days of randomization. If further treatment was required, argon laser trabeculoplasty was the first option, followed by a sequence of medications, repeat trabeculectomy with an antifibrotic agent, and medications. In the medical arm, patients received a sequence of medications that usually began with a topical beta-blocker, followed by an alternate single topical therapeutic agent, dual topical therapy, triple topical therapy, an alternate combination of triple topical therapy, and optional additional topical and/or oral medications. If further treatment was required, the next treatment step was argon laser trabeculoplasty, followed by trabeculectomy, medications, trabeculectomy with an antifibrotic agent, and medications. Criteria for intervention failure (failure to meet the target IOP or evidence of progressive visual-field loss or both) had to be met before further treatment steps were initiated. The patients were followed up every 6 months for a period of 5 years.

Primary outcome measures were visual-field loss³ and quality of life.⁴ Increasing visual-field scores reflected increasing visual-field loss. Quality of life was assessed using the Symptom and Health Problem Checklist and the Visual Activities Questionnaire (VAQ). Secondary outcome

measures were visual acuity, IOP, and cataract formation.³

There was no significant difference in visual-field loss and quality of life when the two groups were compared after a completed follow-up of 4 years and a partially completed follow-up of 5 years, although the quality of life measure was initially better in the medication group. In addition, there was no significant change in the visual-field scores in both treatment groups compared with baseline values. Patients who had higher visual-field deficits were associated with a greater likelihood of having complaints of dimming of vision, difficulty with distance vision, and difficulty with depth perception. The average VA in the two groups was similar. IOP was lower with surgery (IOP range of 14-15 mm Hg through 5 years from a baseline average of 27 mm Hg) than with medications (IOP range of 17-18 mm Hg through 5 years from a baseline average of 28 mm Hg). Initial surgical treatment had a higher rate of cataract formation requiring removal (17.3%) than initial medical treatment (6.2%). The frequency of treatment crossover was comparable in both the medical (8.5%) and surgical (8.3%) groups. By four years of follow-up, 27.9% in the medical group and 20.8% in the surgical group underwent laser trabeculoplasty (LTP). Supplemental LTP was effective in further lowering IOP in both treatment arms.

COMMENTS

This is a well-conducted, randomized controlled clinical trial involving newly diagnosed glaucoma patients that utilized the concept of individualized target IOP rather than a fixed percentage IOP reduction. Aggressive treatment was used to reach the individualized target IOP in both treatment groups using a set protocol. Effect of glaucoma and its treatment on the quality of life was assessed.

There was no selection bias. By using adaptive randomization called minimization, it achieved an optimal balance between the two treatment groups regarding age, study site, gender, race, and diagnosis.

All available data at all time points were analyzed as randomized. The rates of follow-up were similar in both treatment groups from 6 months to 5 years, minimizing attrition bias.

Study limitations

This study has partially completed follow-up at five years; the last follow-up interval of 161 patients was not included in the analysis. The attrition rates, however, were similar in both treatment groups.

Five-year follow-up might not be long enough to show a difference between initial treatment with surgery versus medications. Other large glaucoma clinical trials (e.g. Ocular Hypertension Treatment Study, Advanced Glaucoma Intervention Study) showed a more significant

difference between their respective treatment groups after 5 years of follow-up.

The patients, doctors, and examiners of the outcome measures were not masked to the treatment allocation, which may result in some performance and detection bias. This was unavoidable in most cases. However, interviewers for the quality of life measures were masked.

The Humphrey total deviation plot was used to detect glaucomatous visual-field defects, which may be confounded by the presence of media opacities (e.g. cataracts).

The disease status of the patients included in this study might be too mild to observe a difference between the two treatment groups.

Glaucoma progression was evaluated by visual-field deterioration alone. This may overlook eyes that had glaucomatous optic-nerve changes that have not manifested functionally on standard automated perimetry. This may lead to underdiagnosis of progression.

Laser trabeculoplasty was not viewed as an intervention with crossover implications.

The quality of life measures may be confounded by other ocular comorbidities.

IMPLICATIONS ON CLINICAL PRACTICE

The current data in this study are insufficient to determine whether medical or surgical therapy is more effective in controlling open angle glaucoma (OAG). However, the results suggest that aggressive therapy to lower IOP to a predetermined individualized target prevents visual-field deterioration in the intermediate follow-up period. Furthermore, the level of IOP reduction (surgical group 44%; medical group 35%) is higher than in some of the other large clinical trials (e.g. Early Manifest Glaucoma Trial, Collaborative Normal-Tension Glaucoma Study, Ocular Hypertension Treatment Study), which may explain why none of the eyes in this study had any significant visual-field progression. Thus, an individualized target IOP should be established for glaucoma patients based on the severity of their disease, baseline IOP and other factors. All treatment efforts should then be exerted to reach, maintain and, if needed, adjust the target IOP to prevent the progression of glaucoma.

The advent of a potent class of glaucoma medications (prostaglandin analogues/ocular hypotensive lipids) has allowed greater lowering of IOP compared with older drugs, enabling ophthalmologists to reach treatment goals medically in a substantial number of cases. If the IOP is still not controlled with maximum tolerated medical therapy, laser trabeculoplasty and surgery are other options to control the disease. As shown in this study, laser trabeculoplasty is an effective adjunctive modality to further lower the IOP in open-angle glaucoma patients, whether medical or surgical therapy was initially utilized.

In patients who cannot afford the cost of chronic medical therapy or in whom compliance is a problem, trabeculectomy is a viable alternative as initial treatment. However, they should be warned of the higher rate of developing cataracts, which may negate the cost-effectiveness of surgical therapy.

The quality of life of patients with glaucoma appears to be negatively affected with increasing severity of the disease. It is essential that ophthalmologists educate these patients regarding the nature of their disease and provide them optimal treatment to lessen the impact on the quality of life.

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Advanced Glaucoma Intervention Study (AGIS)¹

Reviewed by Jesus Altuna, MD

STUDY SUMMARY

The Advanced Glaucoma Intervention Study is a multicenter, prospective, randomized study on advanced primary open-angle glaucoma patients (POAG) that have failed initial medical treatment. The study assessed the outcomes of sequences of interventions involving trabeculectomy and argon laser trabeculoplasty. Specifically, the association between control of intraocular pressure (IOP) in the two treatment sequences and visual field preservation was determined.

Patients with advanced open-angle glaucoma aged 35 to 80 years old were enrolled into the study. Eligible eyes had to be phakic, on maximum tolerated medical therapy, with best corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score of at least 56 letters (Snellen equivalent approximately 20/80 or 6/24, consistently elevated intraocular pressures of 18 mm Hg or greater, glaucoma visual-field defect score ranging from 1 to 16, and optic disk rim narrowing. Visual-field defect scores derived from Humphrey 24-2 threshold fields were developed for this study and range from 0 (no defect) to 20 (end-stage glaucoma).

Eyes were randomly assigned to one of two sequences of glaucoma interventions: initial argon laser trabeculoplasty followed by trabeculectomy and trabeculectomy (ATT), and initial trabeculectomy followed by argon laser trabeculoplasty and trabeculectomy (TAT).

The outcome measure is a change from baseline in follow-up of visual-field defect score. The relationship between intraocular pressure (IOP) and progression of visual-field damage over 6 or more years of follow-up was determined.

The AGIS 7 report can be viewed as a dose-response analysis. Two analyses were used by the investigators. In the predictive analysis, the "dose" was the average IOP from the first three 6-month visits. In the associative analysis, the "dose" was the percent of visits over 6 years at which the treated eye achieved target IOP (<18 mm Hg). The response for both analyses was visual-field progression. The predictive analysis was designed to assess whether IOP during early follow-up is predictive of subsequent change from baseline in visual-field defect score. Seven hundred thirty eight eyes were categorized into three groups in accordance with the average IOP over the 6th, 12th, 18th month visits: Group A (<14 mm Hg), Group B (14-17.5 mm Hg) and Group C (>17.5 mm Hg). The associative analysis is a measure of consistency of IOP control. Five hundred eighty six eyes were further categorized into four groups based on the percent of 6-month visits over the first 6 follow-up years in which eyes presented with IOP less than 18 mm Hg: Group A (100%), Group B (>75% - <100%), Group C (50% - 75%) and Group D (0% - <50%).

In the predictive analysis, eyes with average IOP greater than 17.5mm Hg had an estimated worsening during subsequent follow-up that was 1 unit of visual-field defect score greater than eyes with average IOP less than 14 mm Hg ($p = 0.002$). This amount of worsening was greater at 7 years (1.89 units; $p < 0.001$) than at 2 years (0.64 units; $p = 0.071$). In the associative analysis, eyes with 100% of visits with IOP less than 18 mm Hg over 6 years had mean changes from baseline in visual-field defect score close to zero during follow-up, whereas eyes with less than 50% of visits with IOP less than 18 mm Hg had an estimated worsening over follow-up of 0.63 units of visual-field defect score ($p = 0.083$). This degree of worsening was greater at 7 years (1.93 units; $p < 0.001$) than at 2 years (0.25 units; $p = 0.572$).

COMMENTS

This study has a long follow-up period of up to 7 years with a large sample size of 591 patients (789 eyes). Standardized protocol was followed in all the different centers participating in the study. Eligibility measurements were separated from baseline measurements obtained for all patients once they were randomized to the two treatment sequences.

Study limitations

Predictive and associative analyses were not part of the original protocol but added afterwards. Bias may therefore be introduced into the analyses. Moreover, only one visual field was obtained to document baseline glaucomatous defects prior to treatment. Several studies^{2,3} have shown the necessity of obtaining several visual fields as baseline, due to the short-term fluctuation present in threshold sensitivities.

In the analyses, the cases were not stratified according to the degree of glaucoma damage. In spite of the title "Advanced Glaucoma," advanced cases with visual-field defect score greater than 16 were excluded. Early cases of glaucoma were also included because the inclusion criteria of the visual-field defect score ranged from 1 to 16.

Responses to the two treatment sequences described were among the white and black patients. This may not apply to patients from other ethnic groups.

IMPLICATIONS ON CLINICAL PRACTICE

The AGIS showed that early response to treatment predicts a more favorable outcome. The predictive analysis

suggests that patients who achieved the target IOP following initial intervention have better preservation of the visual field. Conversely, those who have not achieved target IOP after 6 months did worse. It is worthy to note that when IOP is more resistant to surgical or medical intervention, the outcome is generally worse. Low IOP is desirable as long as complications are avoided or kept to a minimum. The risk-to-benefit ratio of any treatment should always be weighed by both physician and patient. The treatment objective should always be individualized.

An important issue for any study to address is clinical applicability. The AGIS study does not apply to all glaucoma patients, but is limited to advanced POAG. Glaucoma patients from other ethnic groups may also have different responses to the surgical treatment programs used in AGIS.

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Objective: State the purpose or objective of the study.

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Number the pages of the manuscript consecutively, beginning with the title page as page one. The text should, in general, not exceed 18 double-spaced typewritten pages.

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- Setting: (e.g. multi-center, institutional, clinical practice, etc)
- Participants, Patients or Study Population: Number of patients/eyes, selection procedures, inclusion/exclusion criteria, randomization procedure, and masking.
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Journal Article (If five or more authors, list only the first three and add et al):

Vail A, Gore SM, Bradley BA, et al. Clinical and surgical factors influencing corneal graft survival, visual acuity, and astigmatism. *Br J Ophthalmol* 1996; 103: 41-49.

Chapter in a Book

Parks MM, Mitchell PR. Cranial nerve palsies. In: Tasman W, Jaeger EA, eds. *Duane's Clinical Ophthalmology*, revised ed. Philadelphia: JB Lippincott, 1993; v. 1, chap. 19: 550-551.

Book

Miller NR. *Walsh and Hoyt's Clinical Neuro-Ophthalmology*, 4th ed. Vol. 4. Baltimore: Williams & Wilkins, 1991; 2102-2114

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World Health Organization. Hospital infection control guidelines for severe acute respiratory syndrome. April 16, 2003: <http://www.who.int/csr/sars/infectioncontrol/en> (accessed April 24, 2003).

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