Journal of the South East Asia Glaucoma Interest Group

Volume 7, Number 3, 2005

Asian Journal of OPHTHALMOLOGY

Intraocular Pressure-independent Risk Factors for Glaucoma

Bimatoprost for Glaucoma and Ocular Hypertension

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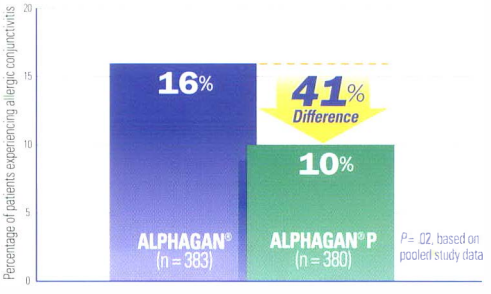

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As new technologies and therapeutic interventions are continually being developed, ophthalmology has become a field of rapid change, particularly in the Asia-Pacific region, where disease patterns and health care delivery differ greatly from those seen in the West. Asian Journal of OPHTHALMOLOGY was established in 1998 and became the official journal of SEAGIG in 2003, with the aim of disseminating information relevant to ophthalmology and glaucoma throughout Asia and to interested groups worldwide. The objectives of Asian Journal of OPHTHALMOLOGY are as follows:

- to provide a platform for the publication of information with a focus on ophthalmology in Asia
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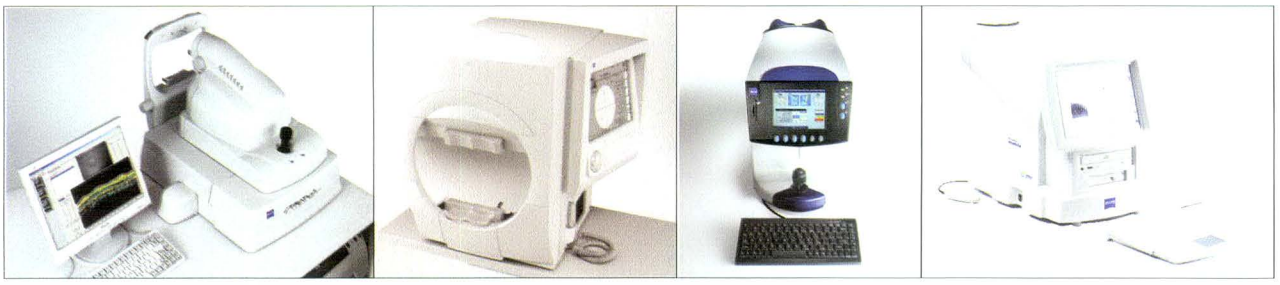

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Clinical Trials in Asia

In this issue of Asian Journal of OPHTHALMOLOGY, Rait et al report their findings from a clinic-based assessment of the safety and efficacy of bimatoprost for managing ocular hypertension and open angle glaucoma in the Asia Pacific region.[1] The study aims to inform general ophthalmologists of the benefits and possible adverse effects of using bimatoprost to treat the broad range of patients in their practices. Rait et al rightly point out that research protocols used in glaucoma clinical trials, and in particular the enrolment criteria, often stipulate the ability to reproducibly perform visual field tests to very high standards, or that patients should have clear ocular media allowing high-quality disc photography. Such conditions are necessary when attempting to answer specific scientific questions. However, they do limit the generalisability of data to the usual patients seen in clinical practice, who may have some lens opacity and may not be able to perform visual field tests to consistently high standards. This study is deliberately inclusive, involving 1954 patients of 195 ophthalmologists in 168 practices, spanning 6 different countries. Patients were excluded only if they had a history of adverse reaction to one of the components of the eye drop, or if there was a clear relative contraindication. The outcome measures were change in intraocular pressure (IOP) and adverse events. One might question whether lack of measures such as calibration of equipment, standardisation of observers and methods, and possible variations in the thresholds of reporting side effects will have influenced the results. It seems unlikely that any of these factors will have exerted a systematic bias to drive the results consistently in one direction. More likely, if they did occur, they will have increased the variability of results (making a true effect more difficult to detect). Clearly this was not a hindrance, as highly significant reductions in IOP were demonstrated for monotherapy, replacement therapy, and adjunctive therapy.

The authors point to the role of studies such as this as a method of surveillance and audit of the safety of medications. Topical non-selective β-blockers are still widely used for the management of glaucoma. Their respiratory side effects can cause significant disability and often go unrecognised.[2]

The authors highlight safety issues relating to the recent withdrawal of rofecoxib, a cyclooxygenase-2 inhibitor used for the treatment of arthritis, which was found to be associated with a more than 2-fold increased risk of serious cardiovascular side effects compared with a standard non-steroidal anti-inflammatory drug.[3] In an editorial in the *British Medical Journal*, experts call for various safety measures to be put in place, including the imposition of clear 'financial firewalls' between pharmaceutical companies and researchers performing systematic reviews and clinical studies. This is clearly the counsel of perfection. However, without the patronage and sponsorship of the company marketing bimatoprost, this very worthwhile study would almost certainly not have been possible. Pharmaceutical and medical equipment industries play an increasingly prominent and important role in supporting continuing medical education and in funding research. With the development of economies in the Asia Pacific region, and increasingly high costs of medical research in Europe and the USA, it seems likely that medical research will become increasingly prominent in the region. The best way of financing and promoting high-quality research that addresses important questions in an unbiased manner is not clear, but it is an issue that needs to be addressed.

References

1. Rait JL, Low CH, Leuenberger EU, et al. Efficacy and safety of bimatoprost in patients with open angle glaucoma or ocular hypertension in the Asia Pacific region. Asian J Ophthalmol 2005;7:82-90.
2. Diggory P, Cassels-Brown A, Vail A, Abbey LM, Hillman JS. Avoiding unsuspected respiratory side-effects of topical timolol with cardioselective or sympathomimetic agents. Lancet 1995;345:1604-1606.
3. Dieppe P, Ebrahim S, Martin RM, Juni P. Lessons from the withdrawal of rofecoxib. BMJ 2004;329:867-868.

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Intraocular Pressure–independent Risk Factors for Progression of Glaucoma

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Although intraocular pressure is the most widely studied risk factor for progression of open angle glaucoma, there is growing evidence that other factors may affect the prognosis of this disease. Among the intraocular pressure–independent risk factors, disc haemorrhage and peripapillary atrophy have been associated with progression of open angle glaucoma. There is a relationship between the location of the disc haemorrhage and the area of progression of visual field loss. Peripapillary atrophy occurs more frequently in eyes with glaucoma than in healthy eyes. This paper reviews the evidence suggesting that disc haemorrhage and peripapillary atrophy may be independent prognostic factors for progression of glaucoma.

Key Words: Atrophy, Glaucoma, open angle, Hemorrhage, Optic disk, Prognosis, Risk Factors

Asian J Ophthalmol 2005;7(3):78-81.

Introduction

Intraocular pressure (IOP) is undoubtedly the most significant risk factor for the progression of optic disc damage and visual field defect in open angle glaucoma (OAG) and normal tension glaucoma (NTG). However, there is growing evidence that ocular factors other than IOP affect the prognosis of OAG. Ocular risk factors for glaucoma progression can therefore be divided into 2 groups of IOP-dependent and IOP-independent risk factors. Disc haemorrhage and peripapillary atrophy are the 2 most important IOP-independent risk factors for progression.

Features of Disc Haemorrhage

Disc haemorrhage is not uncommon in OAG, with a reported prevalence rate of 20% in NTG. In Japan, the prevalence rate of disc haemorrhage is reported to be 20.5% in NTG, 4.2% in OAG, and 0.4% in non-glaucomatous eyes (Table 1).[1] In this study, disc haemorrhage was not noted in eyes with angle closure glaucoma (ACG).

Disc haemorrhage is a transient condition, lasting for a few weeks to several months.[2] It is possible that the limited duration of each episode of disc haemorrhage contributes to underestimates of the prevalence rate. The probability of occurrence of disc haemorrhage is 38.4% for NTG and 16.9% for OAG in 11 and 14 years, respectively.[3]

It has been noted that disc haemorrhage occurs most frequently in the inferotemporal margin of the disc, with the inferonasal side of the disc being least involved.[2] The appearance of notching of the neuroretinal rim at the site of the disc haemorrhage has been observed.

Recurrence is another important characteristic of disc haemorrhage, and it occurs in 12% to 64% of patients with glaucoma.[1,2] Kitazawa et al noted that 18 of 28 eyes with disc haemorrhage (64%) had recurrent episodes.[1] The number of recurrences ranged from 1 to 7. In 13 eyes (72%), the recurrent haemorrhages occurred in the same quadrant of the optic disc where the previous haemorrhages had been present. This finding was also described by Shihab et al in 3 of 25 patients who had disc haemorrhage.[2] This is clinically important because disc haemorrhage tends to precede the deterioration of visual field and indicates an unfavourable prognosis.

Disc Haemorrhage as a Risk Factor for Progression

In 1998, Ishida et al reported that disc haemorrhage was a risk factor for the rate of visual field progression in NTG. In this study of 110 patients with NTG, several clinical factors were investigated to find a possible association with progression of glaucomatous visual field.[4] Change in the visual field was found to be significantly associated with treatment with calcium channel blockers, recovery rate from a cold recovery test, systolic blood pressure, disc haemorrhage, corrected pattern standard deviation, mean deviation, and diurnal fluctuation of IOP. These authors concluded that factors other than IOP are associated with visual field loss in NTG.

This conclusion was supported by the finding that the rate of visual field progression is significantly higher in eyes with NTG with disc haemorrhage than in

Table 1. Prevalence of disc haemorrhage in glaucoma in Japan.

Glaucoma type	Number of patients/Total (%)
Primary open angle glaucoma	8/192 (4.2)
Normal tension glaucoma	16/78 (20.5)
Primary angle closure glaucoma	0/113 (0)
Ocular hypertension	1/204 (0.5)
Healthy eyes	2/473 (0.4)

This paper was presented in part at the 20th Asia Pacific Academy of Ophthalmology Congress, Kuala Lumpur, Malaysia, 28 March 2005.

Table 2. Progression of eyes with and without disc haemorrhage according to mean deviation definition and pointwise definition of progression.

	Eyes with disc haemorrhage (n = 32)	Eyes without disc haemorrhage (n = 38)	p Value
Mean deviation definition	17	4	0.0002
Pointwise definition	26	17	0.004

Table 3. Progression of eyes with and without recurrent disc haemorrhage according to mean deviation definition and pointwise definition of progression.

	Eyes with 1 disc haemorrhage (n = 9)	Eyes with ≥2 disc haemorrhages (n = 23)	p Value
Mean deviation definition	4	13	
Probability of no further visual field deterioration (%)	67 ± 16	27 ± 13	
Pointwise definition	3	23	0.0001
Probability of no further visual field deterioration (%)	42 ± 17	0 ± 0	

those without disc haemorrhage and that recurrent disc haemorrhage indicates a higher probability for the visual field to deteriorate.[5] Ishida et al investigated the relationship between disc haemorrhage in NTG and the progression of visual field defects in 70 eyes of 70 patients to determine the extent to which progression of visual field loss in NTG is affected by disc haemorrhage.[5] Disc haemorrhage, age, corrected-pattern standard deviation, systolic blood pressure, and pulse rate were found to be significant risk factors for visual field progression.

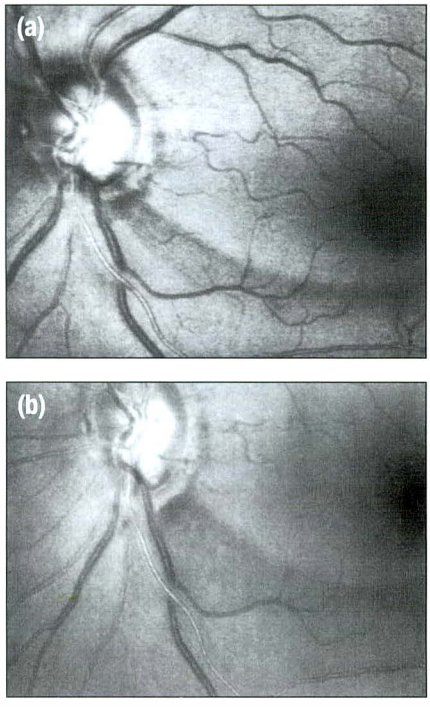
When eyes were divided into 2 subgroups according to the presence or absence of disc haemorrhage, significantly more eyes with disc haemorrhage progressed than eyes without disc haemorrhage (Table 2). Similarly, progression was shown in more eyes with recurrent disc haemorrhage (≥2 occurrences) than in eyes with only 1 disc haemorrhage (Table 3). In addition, there was a significant relationship between the location of the disc haemorrhage and the area of progression of visual field loss in 65.4% of patients with disc haemorrhage who progressed. These findings suggest that disc haemorrhage is a significant negative prognostic factor for patients with NTG and may be a sign of progressive damage of the retinal nerve fibre layer (RNFL), leading to functional deterioration of the visual field.

In 2001, Drance et al clearly demonstrated a higher rate of visual field progression in eyes with disc haemorrhage than in eyes without disc haemorrhage.[6] Visual field data from 160 eyes of 160 patients enrolled in the Collaborative Normal Tension Glaucoma Study showed that the presence of disc haemorrhage affected the subsequent course of visual field deterioration.[6] The mean time to demonstrable progression for eyes without an initial disc haemorrhage was 2159 ± 109 days compared with 1187 ± 196 days for eyes with a baseline disc haemorrhage ($p = 0.0034$). The adjusted odds ratio for the presence of a baseline disc haemorrhage was 2.72 (95% confidence interval, 1.39-5.32). The presence of disc haemorrhage signifies an additional risk factor for progression.

Disc haemorrhage often occurs at, or close to, the border of the retinal nerve fibre layer defect (RNFLD). In a study of the topographic correlation between optic disc haemorrhage and RNFLD, Sugiyama et al evaluated the relationship between the precise locations of disc haemorrhage and RNFLD in 42 patients with NTG.[7] Sixty four disc haemorrhages were noted in 48 eyes of 42 patients and RNFLDs were observed in 47 of the 48 eyes. Of the 64 disc haemorrhages, 51 coincided with the location of RNFLDs, in that the 51 disc haemorrhages were present on the border or adjacent to the border between the RNFLD and the apparently healthy-looking RNFL. The clinical significance of this finding is that disc haemorrhage might indicate the location of an RNFLD even in patients in whom such a defect may be difficult to discern by ophthalmoscopy. Figure 1 demonstrates an RNFLD 5 years after a disc haemorrhage.

A later study in which Sugiyama et al evaluated the frequency of localised wedge-shaped defects of the RNFL in 83 eyes with NTG and in 20 eyes with OAG with and without disc haemorrhage confirmed this finding.[8] Localised wedge-shaped defects of the RNFL occurred significantly more often among patients with disc haemorrhage than among those without disc

Figure 1. Enlargement of cupping and retinal nerve fibre layer defect during a 5-year period. (a) A small splinter haemorrhage is present at the 5-o'clock position in December 1995; and (b) the retinal nerve fibre layer defect is widened in August 2000. Photograph courtesy of Dr Kazuhisa Sugiyama.



haemorrhage in both NTG ($p < 0.0001$) and OAG ($p < 0.05$). Most disc haemorrhages were present in the vicinity of the border between the localised RNFLDs and relatively healthy-looking RNFL in eyes with POAG and those with NTG.

While IOP is the most extensively studied intrinsic ocular factor, the aetiology of disc haemorrhage remains to be elucidated. However, studies have shown that disc haemorrhage is more likely to develop at a relatively lower IOP during therapy with ocular hypotensive agents.[9] The reason for this phenomenon may be that IOP reduction causes anterior displacement of the lamina cribrosa, thereby increasing venous resistance; an increase in the pressure difference across the vascular wall; and changes in haemodynamic factors, possibly leading to haemorrhage.

The presence of disc haemorrhage is thought to indicate an ongoing, active process that damages the optic disc in OAG.[1] Therefore, disc haemorrhage may be a useful and reliable indicator to distinguish patients who have progressive visual field loss from those who are less likely to progress, and may thus be clinically helpful for developing a management plan for patients with OAG.[5]

Peripapillary Atrophy as a Risk Factor for Progression

Peripapillary atrophy is also believed to be an IOP-independent risk factor for progression of glaucoma. It is widely accepted that peripapillary atrophy is more frequent and more extensive in patients with glaucoma than in healthy individuals.[10] Associations have been detected between the extent of peripapillary atrophy and the amount of optic disc damage, and between the location of peripapillary atrophy and the location of both optic disc damage and visual field defects.

In OAG, both structural and functional disc changes are closely related to the size of peripapillary atrophy.[10] In a study to determine the incidence and degree of progression of peripapillary atrophy in 75 eyes with progressive and non-progressive glaucoma, Uchida et al found that 28 eyes (37%) showed progression of peripapillary atrophy.[10] Thirty three eyes (44%) showed progressive optic disc damage. Twenty one of the 33 eyes with progressive disc damage (64%) showed progression of peripapillary atrophy compared with 7 of 42 eyes without progressive disc damage (17%) [$p < 0.01$].

Table 4. Optic disc progression and visual field progression in patients with and without progressive peripapillary atrophy.

	Progressive peripapillary atrophy	Non-progressive peripapillary atrophy
Optic disc progression	75%	26%
Visual field progression	54%	11%

Optic disc progression and visual field progression were both significantly more frequent among patients with progression of peripapillary atrophy than among those without progression of peripapillary atrophy ($p < 0.01$; Table 4). No correlation was found between progression of peripapillary atrophy and mean IOP. These findings suggest that progression of peripapillary atrophy is associated with progressive optic disc damage and progressive visual field loss in glaucoma and may be a useful marker for progressive glaucomatous damage.

The size of peripapillary atrophy relative to that of the disc and the cup-disc ratio is significantly greater in eyes with disc haemorrhage than in those without disc haemorrhage.[11] Peripapillary atrophy therefore appears to be associated with a higher degree of cupping of the optic disc and disc haemorrhage.

Hayakawa et al investigated the association of the peripapillary atrophy area with disc cupping area and disc haemorrhage in 8842 eyes of 4421 people undergoing a routine health examination.[11] The ratio of cup area to disc area was significantly greater in eyes with peripapillary atrophy (0.36 + 0.09) than in eyes without peripapillary atrophy (0.34 + 0.07), and the ratio of peripapillary atrophy area to disc area was significantly greater in eyes with disc haemorrhage (0.26 + 0.34) than in those without disc haemorrhage (0.09 + 0.18). Moreover, in eyes with peripapillary atrophy, the ratio of cup area to disc area was significantly larger in eyes with disc haemorrhage (0.48 + 0.08) than in those without disc haemorrhage (0.36 + 0.09). These results suggest an association between peripapillary atrophy and glaucomatous optic neuropathy.

Sugiyama et al studied the association of peripapillary atrophy and disc haemorrhage in patients with NTG.[7] These authors found that 39 of 40 eyes (97.5%) with disc haemorrhage had peripapillary atrophy compared with 42 of 51 eyes (82.4%) with no disc haemorrhage ($p = 0.0385$). The area, angular extent, and ratio of peripapillary atrophy area to disc area were significantly greater in eyes with disc haemorrhage than in eyes without disc haemorrhage ($p = 0.0446$, $p = 0.0263$, and $p = 0.0246$, respectively). These findings suggest a significant association between disc haemorrhage and peripapillary atrophy in NTG.

Uchida et al noted different peripapillary atrophy characteristics between eyes with ACG and eyes with OAG, suggesting different pathological processes of glaucomatous change for the 2 types of glaucoma.[12] Eight of 21 eyes with ACG (38%) and 21 of 31 eyes with OAG (68%) had peripapillary atrophy ($p = 0.048$). The ratio of peripapillary atrophy area to disc area of eyes with OAG was significantly larger than

that of eyes with ACG ($p = 0.005$). There was no significant correlation between the ratio of peripapillary atrophy area to disc area and the ratio of cup area to disc area or visual field mean deviation in eyes with ACG. However, there was a significant correlation between the peripapillary atrophy area to disc area and the ratio of cup area to disc area ($p = 0.003$) and the visual field mean deviation ($p < 0.001$) in the eyes with OAG.

Although little is known about the pathogenesis of peripapillary atrophy, and further study is required, progression of peripapillary atrophy is associated with progressive glaucomatous damage and may provide clinically relevant information about the status of glaucomatous optic nerve damage.

References

1. Kitazawa Y, Shirato S, Yamamoto T. Optic disc hemorrhage in low-tension glaucoma. Ophthalmology 1986;93: 853-857.
2. Shihab ZM, Lee PF, Hay P. The significance of disc hemorrhage in open-angle glaucoma. Ophthalmology 1982; 89:211-213.
3. Kitazawa Y. Open-angle glaucoma clinical presentation and management. J Jpn Ophthalmol Soc 2003;105:828-842.
4. Ishida K, Yamamoto T, Kitazawa Y. Clinical factors associated with progression of normal-tension glaucoma. J Glaucoma 1998;7:372-377.
5. Ishida K, Yamamoto T, Sugiyama K, Kitazawa Y. Disk hemorrhage is a significantly negative prognostic factor in normal-tension glaucoma. Am J Ophthalmol 2000;129:707-714.
6. Drance S, Anderson DR, Schulzer M; Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol 2001;131:699-708.
7. Sugiyama K, Tomita G, Kitazawa Y, Onda E, Shinohara H, Park KH. The associations of optic disc hemorrhage with retinal nerve fiber layer defect and peripapillary atrophy in normal-tension glaucoma. Ophthalmology 1997;104: 1926-1933.
8. Sugiyama K, Uchida H, Tomita G, Sato Y, Iwase A, Kitazawa Y. Localized wedge-shaped defects of retinal nerve fiber layer and disc hemorrhage in glaucoma. Ophthalmology 1999;106: 1762-1767.
9. Drance SM, Begg IS. Sector hemorrhage — a probable acute ischemic disc change in chronic simple glaucoma. Can J Ophthalmol 1970;5:137-141.
10. Uchida H, Ugurlu S, Caprioli J. Increasing peripapillary atrophy is associated with progressive glaucoma. Ophthalmology 1998;105:1541-1545.
11. Hayakawa T, Sugiyama K, Tomita G, et al. Correlation of the peripapillary atrophy area with optic disc cupping and disc hemorrhage. J Glaucoma 1998;7: 306-311.
12. Uchida H, Yamamoto T, Tomita G, Kitazawa Y. Peripapillary atrophy in primary angle-closure glaucoma: a comparative study with primary open-angle glaucoma. Am J Ophthalmol 1999; 127:121-128.

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Efficacy and Safety of Bimatoprost for Patients with Open Angle Glaucoma or Ocular Hypertension in the Asia Pacific Region

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Aim: *Bimatoprost, a new treatment for open angle glaucoma and ocular hypertension, has been studied primarily under stringent clinical trial conditions. However, regulators have stipulated that drugs should also be studied in clinical practice settings. The purpose of this study was to evaluate bimatoprost in clinical practice.*

Patients and Methods: *This multicentre 3-month clinical practice study used an open-label non-comparative prospective design. Ophthalmologists prescribed bimatoprost 0.03% ophthalmic solution as monotherapy, replacement therapy, or adjunctive therapy for 1954 patients with open angle glaucoma or ocular hypertension who required intraocular pressure lowering.*

Results: *Bimatoprost was associated with a significant reduction in intraocular pressure ($p < 0.0001$), whether prescribed as monotherapy (33.3% reduction), replacement therapy (17.7% reduction), or adjunctive therapy (20.9% reduction). Bimatoprost treatment enabled significantly more patients to achieve a low target pressure compared with pre-existing treatment ($p < 0.0001$). Significant reductions in intraocular pressure after bimatoprost treatment occurred regardless of baseline intraocular pressure and among patients whose intraocular pressure had been difficult to control. Bimatoprost was rated highly by patients and ophthalmologists, had a favourable safety profile, and was well tolerated.*

Conclusions: *In a clinical practice setting with a broad range of patients, bimatoprost was well tolerated and provided substantial reductions in intraocular pressure.*

Key Words: Bimatoprost, Glaucoma, open-angle, Intraocular pressure, Ocular hypertension

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This multicentre research study was conducted by 195 investigators at 168 sites in the Asia Pacific region. The participating investigators and institutions are listed in the Acknowledgements section.

Introduction

Glaucoma and ocular hypertension are among the most common pathologies encountered in ophthalmic practice.[1] The challenge of glaucoma in the Asia Pacific region has been emphasised for some time, particularly in terms of the ageing population.[2-4] Research from the Asia Pacific region has shown that within the next 20 years, as the population ages, the incidence of glaucoma and ocular hypertension is predicted to increase 2- to 3-fold.[5,6] Optimal management of these conditions will require new treatments that have been shown, in both clinical trials and clinical practice, to be effective, safe, and well tolerated.[7]

Bimatoprost, a new ocular hypotensive agent, is a synthetic prostamide that has potent intraocular pressure (IOP)-lowering activity.[8] Bimatoprost lowers IOP by increasing the outflow of aqueous humour through the trabecular meshwork and uveoscleral routes.[9-11]

Bimatoprost has been well studied in stringent clinical trial settings. Studies have shown that bimatoprost is more effective than timolol[12-15] and as effective as, or more effective than, latanoprost or travoprost[16-21] for lowering IOP. Furthermore, bimatoprost, as monotherapy or a component of dual therapy, appears to be as effective as, or more effective than, combinations of other IOP-lowering agents.[7,22]

Further study is required to clearly identify how applicable the bimatoprost clinical trial findings are to clinical practice.[7] To date, there has been only 1 published clinical practice study of bimatoprost. In a study performed in the USA, bimatoprost appeared to be clinically effective and well tolerated when used as replacement therapy for latanoprost or as initial monotherapy for 8 weeks.[23,24] Clinical practice studies of new drugs are particularly important for diseases affecting older age groups. In clinical practice studies, in which

eligibility criteria are less stringent than those in clinical trials, the effectiveness of new drugs can be examined against a broader range of coexisting conditions and concomitant medications. Indeed, regulatory authorities have stipulated that clinical practice studies are essential for assessing the optimal use of new drugs.[25] Recent withdrawals of marketed drugs (e.g., rofecoxib) owing to safety issues have reinforced the need for postmarketing surveillance studies.

The purpose of this study was to evaluate the efficacy and safety of bimatoprost for patients with open angle glaucoma or ocular hypertension in a clinical practice setting. In this open-label non-comparative 3-month surveillance study in the Asia Pacific region, participating ophthalmologists selected patients to treat with bimatoprost as monotherapy, replacement therapy, or adjunctive therapy.

Patients and Methods

Study Design and Setting

This study was designed to enable a large-scale community-based prospective evaluation of the safety and efficacy of bimatoprost for the treatment of glaucoma and ocular hypertension. A multicentre open-label non-comparative surveillance design was used. The study involved 195 ophthalmologists at 168 clinical practice sites in 6 countries (Australia, Malaysia, New Zealand, The Philippines, Singapore, and Thailand).

Patients

All patients provided voluntary written informed consent before participating in the study. Patients with open angle glaucoma or ocular hypertension who required reduction of elevated IOP were eligible for participation in the trial. Exclusion criteria were any known allergy to bimatoprost or any of the formulation's components, and any other condition that would make the risk of bimatoprost treatment outweigh its benefits in the opinion of the ophthalmologist (e.g., pregnancy and lactation).

Treatment Protocol

Patients were evaluated according to each ophthalmologist's standard clinical practice. One or both eyes were assessed for each patient. Before treatment, target IOP levels were set for each patient on the basis of their assessed risk of progressive visual damage. Patients received treatment with bimatoprost 0.03% (Lumigan®, Allergan, Irvine, USA) ophthalmic solution as monotherapy (for treatment-naïve patients), replacement therapy (previous treatments replaced by bimatoprost), or as adjunctive therapy (bimatoprost added to the previous treatment regimen). At each visit, patients were provided with one 3-mL bottle of bimatoprost 0.03%, which was sufficient for 1 month of treatment. One drop of medication was applied to each affected eye once daily in the evening for 3 months.

Clinical Evaluation

All patients were scheduled for review at baseline, and after 1, 2, and 3 months of treatment. The primary efficacy variables were measures of IOP and satisfaction with bimatoprost. During each visit, IOP was measured according to the ophthalmologists' standard clinical practice. The ophthalmologists and patients assessed satisfaction at the 3-month visit. The ophthalmologists made an overall assessment and rated bimatoprost against other IOP-reducing medications (on a 4-point scale ranging from poor to excellent). Patients completed a self-evaluation, and stated whether they would use bimatoprost in the future for treatment of their elevated IOP. Patients were also asked to rate the ocular comfort of bimatoprost compared with other treatments previously used (on a 5-point scale ranging from very uncomfortable to very comfortable). All adverse events that occurred during the study were recorded.

Statistical Analysis

Descriptive statistics are reported. For patients receiving bimatoprost treatment in both eyes, a single IOP, based on the mean IOP from both eyes, was used for the analysis. Mean IOP values at each time point, in each group, were compared with the baseline. Probability values were calculated using a paired sample *t* test (with $p < 0.05$ considered significant). Percentages of patients in each group achieving defined IOP values were calculated for each time point. Probability values for the comparison of percentage values were calculated using the Chi squared test (with $p < 0.05$ considered significant). Unless otherwise specified, bimatoprost treatment refers to results obtained from the pooled bimatoprost monotherapy, replacement therapy, and adjunctive therapy groups.

Results

Patient Demographics

The study involved 1954 patients from Australia (n = 769), Thailand (n = 458), Malaysia (n = 317), The Philippines (n = 184), New Zealand (n = 161), and Singapore (n = 65). Most patients had a diagnosis of open angle glaucoma, were older than 50 years, and had IOPs that were difficult to control (Table 1). Three-month data were available for 1397 patients who completed the study (72%). Of the patients who did not complete the study (n = 557), 8.1% (n = 159) withdrew because of adverse events, 8.4% (n = 165) were lost to follow-up, 4.1% (n = 80) withdrew for 'other' reasons or lack of efficacy, and 7.8% (n = 153) had no data explaining their withdrawal.

Effect of Bimatoprost on Intraocular Pressure

Bimatoprost treatment was associated with a significant reduction in IOP, whether

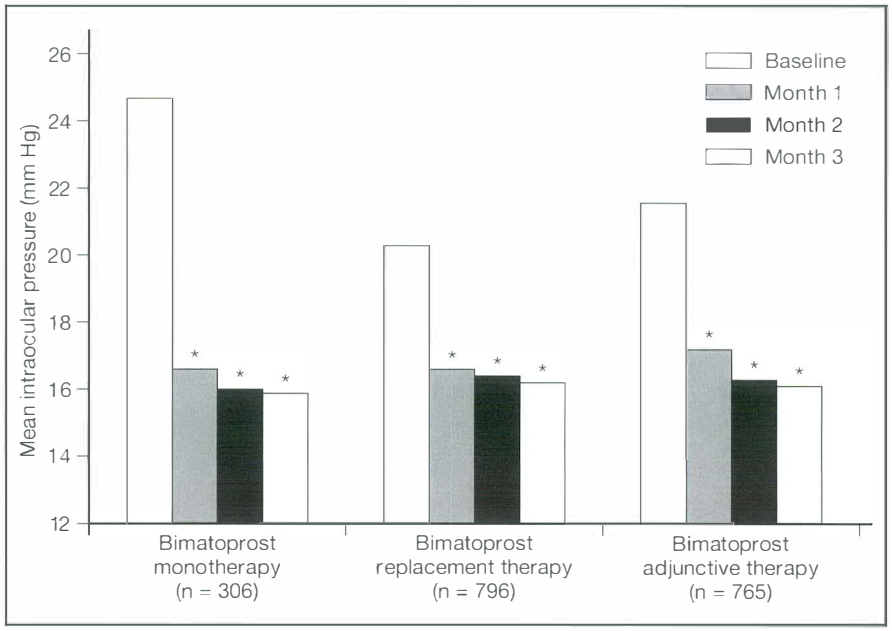
Table 1. Patient demographics and baseline characteristics.

Characteristic	Number (%)
Age (years)	
≥50	1692 (86.6)
<50	262 (13.4)
Sex	
Female	1000 (51.2)
Male	954 (48.8)
Race	
Asian	1057 (54.1)
Black	15 (0.8)
Caucasian	860 (44.0)
Other	22 (1.1)
Diagnosis	
Open angle glaucoma	1747 (89.4)
Ocular hypertension	207 (10.6)
Intraocular pressure at time of enrolment*	
Very difficult to control	107 (5.5)
Difficult to control	444 (22.7)
Somewhat difficult to control	680 (34.8)
Not difficult to control	414 (21.2)
No previous data	309 (15.8)
Prescribed treatment†	
Bimatoprost monotherapy	314 (16.5)
Bimatoprost replacement therapy	809 (42.6)
Bimatoprost adjunctive therapy	777 (40.9)

* Ophthalmologists rated the difficulty of controlling intraocular pressure on the basis of patients' responses to previous ocular hypotensive therapies.
† Prescription data were not provided for 54 patients.

the drug was prescribed as monotherapy, replacement therapy, or adjunctive therapy (Figure 1). Between the baseline and 3-month visits, the mean reduction in IOP with bimatoprost treatment was 8.8 mm Hg (33.3%; $p < 0.0001$) as monotherapy, 4.1 mm Hg (17.7%; $p < 0.0001$) as replacement therapy, and 5.5 mm Hg (20.9%; $p < 0.0001$) as adjunctive therapy. For each group, bimatoprost treatment produced a significant reduction in IOP within 1 month of starting treatment; this positive effect was sustained over 3 months (Figure 1).

Figure 1. Effect of bimatoprost monotherapy, replacement therapy, and adjunctive therapy on mean intraocular pressure.
*** $p < 0.0001$ compared with baseline.**



Bimatoprost treatment enabled significantly more patients to achieve a low target IOP compared with previous management or treatment regimens (Figure 2).

Subgroup Analyses

Baseline Intraocular Pressure

Bimatoprost treatment provided a significant reduction in IOP, regardless of baseline IOP (Figure 3). The decrease in IOP was evident within 1 month and was sustained for 3 months. Even for patients with a low baseline IOP (≤17.9 mm Hg), bimatoprost treatment was associated with a further lowering of IOP.

Difficult to Control Intraocular Pressure

Bimatoprost treatment was associated with significant reductions in IOP, regardless of how difficult it had been to control IOP in the 6 to 12 months before the study (Figure 4). This reduction in IOP occurred within 1 month and was sustained during the study period.

Medications Replaced with Bimatoprost

Bimatoprost treatment significantly reduced IOP when replacing other ocular hypotensive treatments, including combination therapy (Figure 5). The most frequently replaced medications were latanoprost or topical non-selective β-blockers.

Race

Bimatoprost treatment reduced IOP at each time point, regardless of race. Three months of bimatoprost treatment resulted in a mean IOP reduction from baseline of 5.7 mm Hg in patients from Asian races (54% of the study group) and 5.0 mm Hg in patients of races other than Asian (primarily Caucasian [44%]).

Figure 2. Effect of bimatoprost treatment on the percentage of patients (n = 1906) who achieved a target intraocular pressure.
*** p < 0.0001 compared with baseline for each month of treatment.**

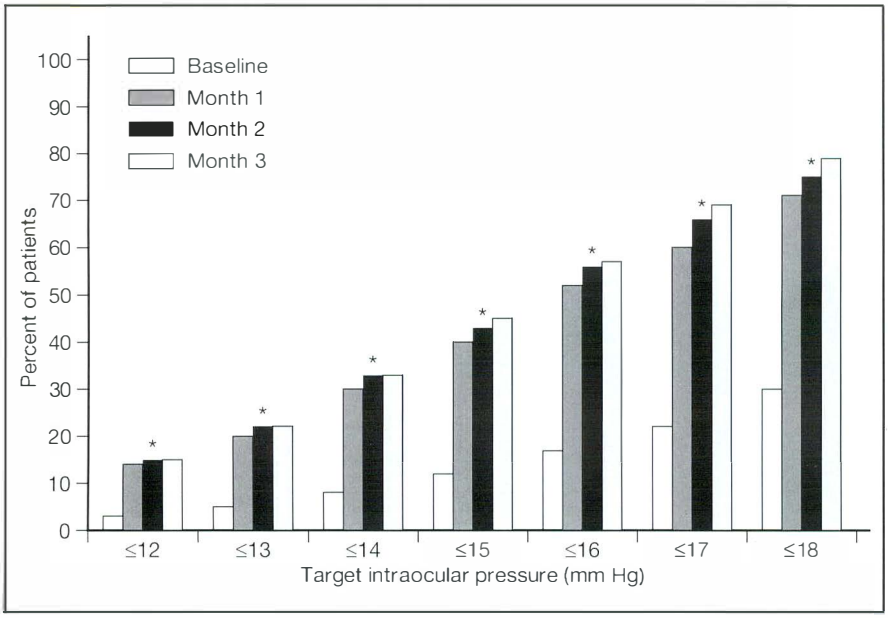
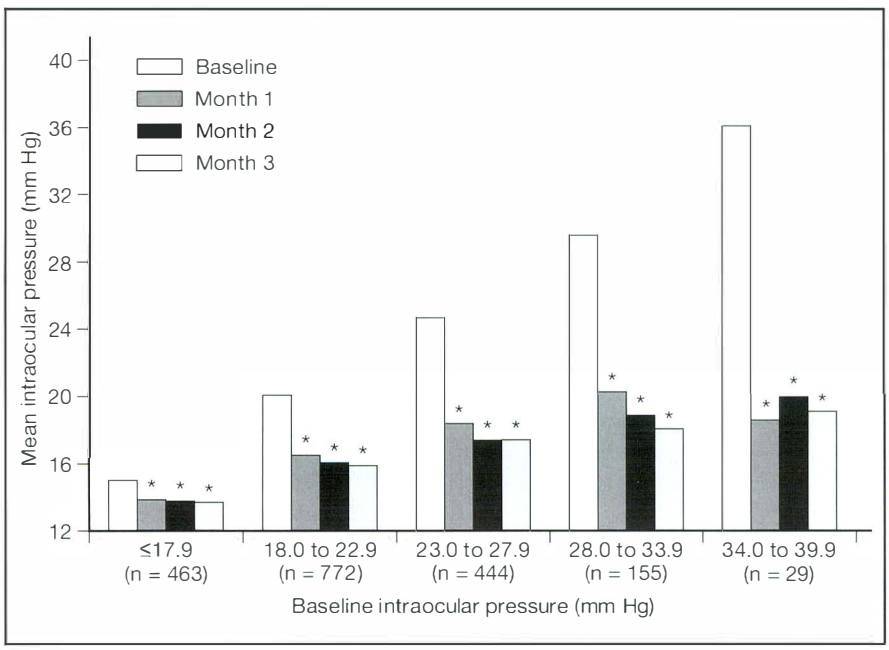


Figure 3. Effect of bimatoprost treatment on intraocular pressure relative to baseline level of intraocular pressure.
*** p < 0.0001 compared with baseline.**



Patient Evaluation

The majority of patients who provided an evaluation of bimatoprost treatment (1079 of 1218 patients; 88.6%) reported that they would use bimatoprost again if it were prescribed, and 82.2% of patients reported that the comfort level of bimatoprost was the same, better, or much better, when compared with the medications previously used.

Clinician Evaluation

The majority of ophthalmologists who provided an evaluation of bimatoprost treatment (126 of 133 ophthalmologists; 94.8%) rated the performance of bimatoprost as 'good' or 'excellent' compared with the ocular hypotensive agents prescribed previously.

Adverse Events

Bimatoprost treatment had a favourable safety profile and was well tolerated. The most commonly reported adverse events (>1% incidence) were conjunctival hyperaemia (12.5%), irritation and burning (4.8%), lid findings (3.0%), and pruritis (2.1%). Most adverse events were mild or moderate in severity. 159 patients (8.1%) discontinued the study because of adverse events. The most common adverse event associated with discontinuation was conjunctival hyperaemia (68 patients; 3.5%).

Discussion

To the best of the authors' knowledge, this is the first study to report the effects of bimatoprost as monotherapy, replacement therapy, and adjunctive therapy in a large cohort of patients from a number of countries in the Asia Pacific region. This study extends the findings from clinical trials, providing clinically relevant information on the effectiveness of bimatoprost in clinical practice. The study shows that bimatoprost treatment can provide substantial and sustained reductions in IOP, whether prescribed as monotherapy, replacement therapy, or adjunctive therapy. Furthermore, this study has shown that clinically relevant reductions in IOP can be consistently achieved across a broad range of patients, including those classified as difficult to treat. In this study, set in clinical practice, bimatoprost had a favourable safety and tolerability profile, with patients and ophthalmologists rating bimatoprost positively in comparison to other ocular hypotensive agents.

The effectiveness of bimatoprost in lowering IOP in this clinical practice study compares well to the efficacy demonstrated

Figure 4. Effect of bimatoprost treatment relative to baseline control of intraocular pressure.
*** p < 0.0001 compared with baseline.**

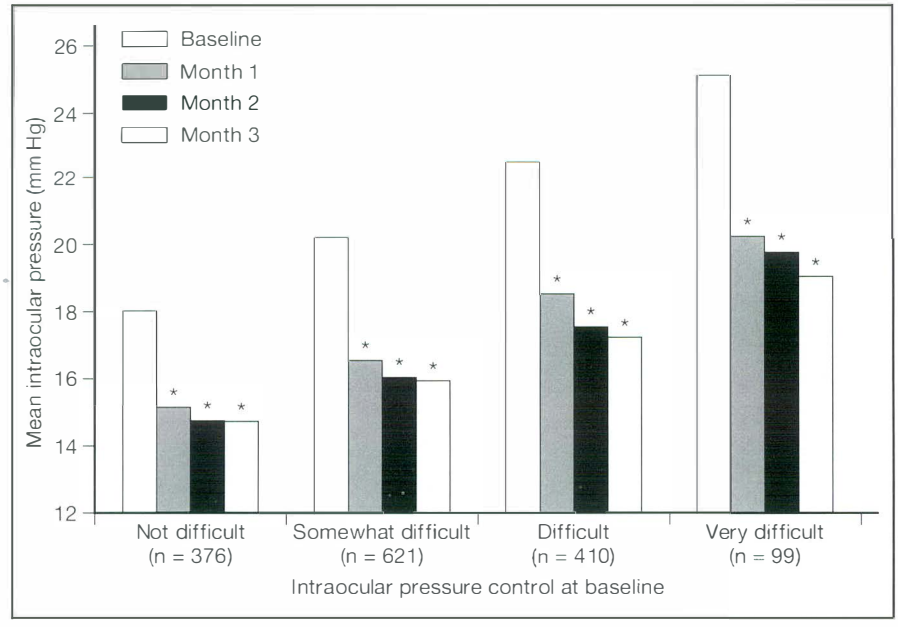
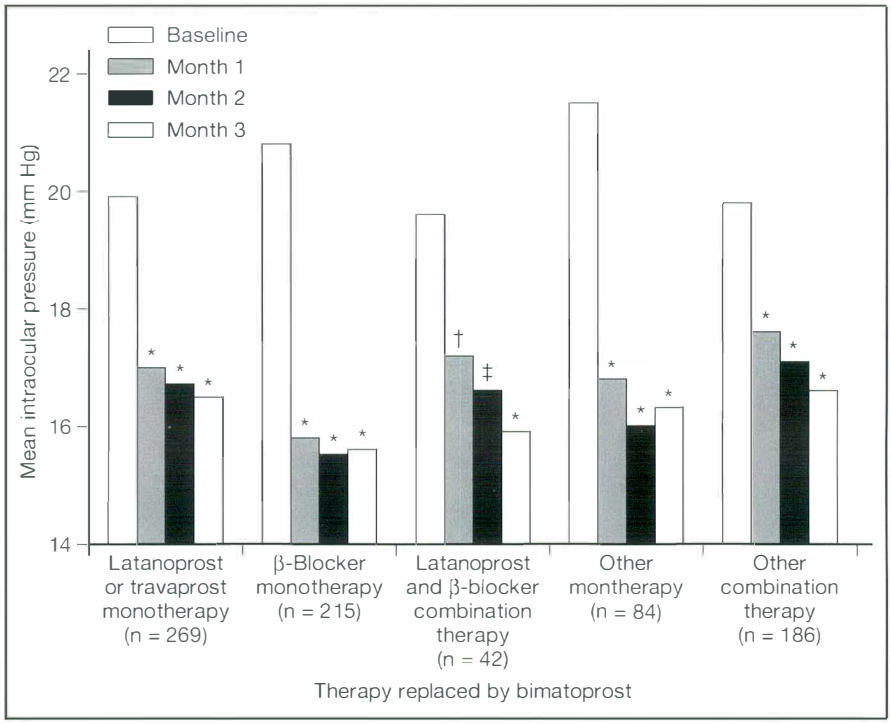


Figure 5. Effect of replacement bimatoprost treatment on intraocular pressure, relative to the previous treatment.
*** p < 0.0001 compared with baseline.**
† p < 0.05 compared with baseline.
‡ p < 0.001 compared with baseline.



in previous randomised controlled clinical trials.[12,13,15,20] This comparability helps to counter criticism that the favourable results achieved in this open-label clinical practice setting may reflect investigator bias. This study has also demonstrated the effectiveness of bimatoprost, whether prescribed as monotherapy, replacement therapy, or adjunctive therapy, for a group of patients with a broad range of baseline IOPs and even for patients with IOPs classified as difficult to control. With a 3-month treatment period, the positive effects that were observed are unlikely to be due to an inadequate wash-out period from the previous agents.

In this study, low target pressures were more likely to be achieved with bimatoprost treatment than with the patients' previous treatments. A low IOP (≤17 mm Hg) is critical to slowing or halting visual field loss in patients with glaucoma.[26,27] Compared with previous treatments, 3 months of bimatoprost treatment enabled 3 times as many patients to achieve a target IOP of 17 mm Hg or lower. This finding is particularly important in clinical practice, where sound justification is required before asking patients to switch medications. The low target pressures achieved in this study compare well to those reported in clinical trials of bimatoprost.[12,13,15,18,21,28]

Limited published information is available on the effectiveness of new ocular hypotensive agents for patients from Asia. Although differences between studies limit direct comparisons, previous studies have shown that patients from India[29] and The Philippines[30] experienced a reduction in IOP with latanoprost treatment.

Similar to other studies,[17,19,23] this study has been able to demonstrate that bimatoprost can provide further reductions in IOP when used as replacement therapy for other ocular hypotensive agents. This finding is consistent with the results of other studies, in which bimatoprost has been shown to provide greater IOP lowering than latanoprost for patients with bilateral glaucoma or ocular hypotension, or normal tension glaucoma.[31,32]

Adverse events recorded during the trial were generally rated as mild to moderate in severity. The most frequent adverse event, conjunctival hyperaemia, has been reported in other studies, and appears to occur more

frequently with bimatoprost than with other ocular hypotensive medications.[7,16,18,21] In a recent investigation of hyperaemia associated with the use of bimatoprost, Abelson et al reported that the severity peaked 24 hours after commencing therapy (84.6% of patients were "hardly/not troubled" by their ocular redness), and returned to near baseline levels by day 28.[33] Hyperaemia was not regarded as a significant safety concern.[33] Although not observed in the study reported here, there has been a single case report of bimatoprost treatment being associated with reactivation of herpes simplex virus keratitis.[34] Caution should be exercised when prescribing phospholipid drugs for patients with a history of keratitis caused by herpes simplex virus.

The patients' and ophthalmologists' evaluations of bimatoprost in this trial were highly favourable. The positive experiences gained with bimatoprost in this study are likely to reflect the broader experiences of patients and ophthalmologists in clinical practice in the Asia Pacific region.

From studying bimatoprost in clinical practice, rather than in a formal clinical trial setting, further questions have arisen that should stimulate clinical discussion and additional research. These questions are as follows:

- Are pressures lowered with bimatoprost low enough? Clinical trials have established that lowering IOP can delay the progression of glaucomatous damage and visual field loss.[26,27,35] Despite the variability in, and prognostic limitations of, IOP, ophthalmologists should strive to lower IOP to a specific target for each patient and maintain that target pressure.[36] Evidence from clinical trials does not define 'how low is low enough' for an individual patient, but evidence from clinical trials and clinical practice indicates that bimatoprost can assist a broad range of patients to achieve their target pressure.[16-24,31,32]
- Should bimatoprost be used as first line treatment? In this study, bimatoprost was associated with clinically relevant reductions in IOP in a broad range of patients, even in patients with IOPs classified as difficult to control and in patients previously treated with other agents. Using first-line bimatoprost therapy to obtain an early, fast, and substantial drop in IOP may be preferable to using bimatoprost to achieve a second drop in IOP when previous agents have not enabled target pressures to be reached. The importance of considering bimatoprost as a first-line option is also reinforced by the results achieved with bimatoprost monotherapy in this study. Bimatoprost monotherapy, as a first-line option, could prove beneficial in terms of convenience, cost, and compliance — issues that are particularly important in general ophthalmic practice.[37,38]

In conclusion, this study, set in clinical practice, demonstrates the efficacy and safety of bimatoprost for treating open angle glaucoma and ocular hypertension in patients from the Asia Pacific region. Bimatoprost was associated with significant reductions in IOP when used as monotherapy, replacement therapy, or adjunctive therapy. Bimatoprost enabled a large number of patients to achieve clinically relevant low target pressures. Bimatoprost was well tolerated, and patients' and ophthalmologists' satisfaction with bimatoprost was high.

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References

1. Mukesh BN, McCarty CA, Rait JL, Taylor HR. Five-year incidence of open-angle glaucoma: the visual impairment project. Ophthalmology 2002;109:1047-1051.
2. Reddy PS. Epidemiology of glaucoma in Asia-Pacific. Yan Ke Xue Bao 1992;8:21-24.
3. Chew PT, Chee CK. An overview of eye problems in Singapore's elderly. Singapore Med J 1991;32:268-270.
4. Goldberg I. Worldwide issues in glaucoma research. Medscape Today 2001. http://www.medscape.com/viewarticle/420835
5. Rait JL. Management of ocular hypertension and primary open angle glaucoma. Clin Exp Optom 2000;83:136-144.
6. Rochtchina E, Mitchell P. Projected number of Australians with glaucoma in 2000 and 2030. Clin Exp Ophthalmol 2000; 28:146-148.
7. Easthope SE, Perry CM. Topical bimatoprost: a review of its use in open-angle glaucoma and ocular hypertension. Drugs Aging 2002;19:231-248.
8. Woodward DF, Krauss AH, Chen J, et al. The pharmacology of bimatoprost (Lumigan®). Surv Ophthalmol 2001;45 (Suppl 4):337-345.
9. Sharif NA, Kelly CR, Crider JY. Human trabecular meshwork cell responses induced by bimatoprost, travoprost, unoprostone, and other FP prostaglandin receptor agonist analogues. Invest Ophthalmol Vis Sci 2003;44:715-721.
10. Cantor LB. Bimatoprost: a member of a new class of agents, the prostamides, for glaucoma management. Expert Opin Investig Drugs 2001;10:721-731.
11. Brubaker RF. Mechanism of action of bimatoprost (Lumigan®). Surv Ophthalmol 2001;45 (Suppl 4):347-351.
12. Whitcup SM, Cantor LB, VanDenburgh AM, Chen K. A randomized, double masked, multicentre clinical trial comparing bimatoprost and timolol for the treatment of glaucoma and ocular hypertension. Br J Ophthalmol 2003;87:57-62.
13. Higginbotham EJ, Schuman JS, Goldberg I, et al; Bimatoprost Study Groups 1 and 2. One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension. Arch Ophthalmol 2002;120:1286-1293.
14. Sherwood M, Brandt J; Bimatoprost Study Groups 1 and 2. Six-month comparison of bimatoprost once daily and twice daily with timolol twice daily in patients with elevated intraocular pressure. Surv Ophthalmol 2001;45 (Suppl 4):361-368.
15. Brandt JD, VanDenburgh AM, Chen K, Whitcup SM; Bimatoprost Study Group. Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP: a 3-month clinical trial. Ophthalmology 2001;108: 1023-1031.
16. Parrish RK, Palmberg P, Sheu WP; XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol 2003; 135:688-703.
17. Gandolfi SA, Cimino L. Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost. Ophthalmology 2003;110:609-614.
18. Noecker RS, Dirks MS, Choplin NT, Bernstein P, Batoosingh AL, Whitcup SM; Bimatoprost/Latanoprost Study Group. A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. Am J Ophthalmol 2003;135:55-63.
19. Williams RD. Efficacy of bimatoprost in glaucoma and ocular hypertension unresponsive to latanoprost. Adv Ther 2002;19:275-281.
20. DuBiner H, Cooke D, Dirks M, Stewart WC, VanDenburgh AM, Felix C. Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: a 30-day comparison with latanoprost. Surv Ophthalmol 2001;45 (Suppl 4):353-360.
21. Gandolfi S, Simmons ST, Sturm R, Chen K, VanDenburgh AM; Bimatoprost Study Group 3. Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. Adv Ther 2001;18:110-121.
22. Netland PA, Michael M, Rosner SA, Katzman B, Macy JI. Brimonidine purite and bimatoprost compared with timolol and latanoprost in patients with glaucoma and ocular hypertension. Adv Ther 2003; 20:20-30.
23. Bournias TE, Lee D, Gross R, Mattox C. Ocular hypotensive efficacy of bimatoprost when used as a replacement for latanoprost in the treatment of glaucoma and ocular hypertension. J Ocul Pharmacol

Ther 2003;19:193-203.
24. Quinones R, Severin T, Mundorf T. Efficacy of bimatoprost 0.03 percent in untreated glaucoma and ocular hypertension patients: results from a large community-based clinical trial. J Ocul Pharmacol Ther 2004;20:115-122.
25. FDA Report to Congress — Reports on Postmarketing Studies. http://www.fda.gov/cber/fdama/ pstmrktfdama130.htm
26. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol 2000;130:429-440.
27. Mao LK, Stewart WC, Shields MB. Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma. Am J Ophthalmol 1991;111:51-55.
28. Noecker RJ, Earl ML, Mundorf T, Peace J, Williams RD. Bimatoprost 0.03% versus travoprost 0.004% in black Americans with glaucoma or ocular hypertension. Adv Ther 2003;20:121-128.
29. Rao BS. Open label, prospective, multi-centre Indian study of latanoprost in primary open angle glaucoma and ocular hypertension. Asian J Ophthalmol 2002; 4:2-5.
30. Aquino MV, Lat-Luna M. The effect of latanoprost vs timolol on intraocular pressure in patients with glaucoma and ocular hypertension. Asian J Ophthalmol 1999;1:3-7.
31. Noecker RJ. Evaluation of bimatoprost 0.03% versus latanoprost 0.005%: a paired comparison study. Invest Ophthalmol Vis Sci 2005;46:E-Abstract 2452.
32. Williams RD, Noecker RJ, Dirks M, Earl M. IOP lowering efficacy of bimatoprost and latanoprost for the treatment of normal tension glaucoma. Invest Ophthalmol Vis Sci 2005;46:E-Abstract 1305.
33. Abelson MB, Mroz M, Rosner SA, Dirks MS, Hirabayashi D. Multicenter, open-label evaluation of hyperemia associated with the use of bimatoprost in adults with open-angle glaucoma or ocular hypertension. Adv Ther 2003;20:1-13.
34. Kroll DM, Schuman JS. Reactivation of herpes simplex virus keratitis after initiating bimatoprost treatment for glaucoma. Am J Ophthalmol 2002;133:401-403.
35. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;126:487-497.
36. Weinreb RN. Lowering intraocular pressure to minimize glaucoma damage. J Glaucoma 2001;10 (5 Suppl 1):76-77.
37. Coons SJ, Sheahan SL, Martin SS, Hendricks J, Robbins CA, Johnson JA. Predictors of medication noncompliance in a sample of older adults. Clin Ther 1994;16: 110-117.
38. Patel SC, Spaeth GL. Compliance in patients prescribed eye drops for glaucoma. Ophthalmic Surg 1995;26:233-236.

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Prevalence of Oblique Insertion of the Arcuate Nerve Fibre Layer Bundle in Normal Eyes and its Influence on GDx Parameters

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Aim: *Anatomical variations of the retinal nerve fibre layer are known to influence GDx parameters, but have not been extensively studied. The aim of this study was to assess the prevalence of oblique insertion of the temporal arcuate retinal nerve fibre bundle at the optic disc and its influence on GDx parameters.*
Patients and Methods: *463 healthy eyes of 234 participants underwent complete ophthalmic examination, including scanning laser polarimetry by GDx. Participants with optic nerve pathology, tilted discs, or split nerve fibre bundles were excluded. The retardation images of the symmetry analysis printouts were analysed by 2 masked observers for oblique or normal insertion of the temporal arcuate nerve fibre bundle, which was confirmed using actual thickness values. An oblique insertion was defined as an arcuate bundle, one-third or more of which crossed the nasal or temporal demarcation lines. A control group of 25 eyes with normal insertion (defined as those in which the bundles lay entirely within the demarcation lines) was selected for comparison. GDx parameters were compared between the groups using Student's* t *test.*
Results: *Sixteen eyes (3.46%) had oblique insertion in the superior quadrant, and 7 (1.51%) in the inferior quadrant. Superior, inferior, and superior/nasal ratios, maximum modulation, nasal and temporal averages, and nasal and temporal medians differed significantly between those eyes with oblique insertion of the nerve fibre bundles and those with normal insertion ($p \leq 0.001$).*
Conclusions: *Oblique insertion of the temporal arcuate retinal nerve fibre bundle was found in 4.97% of eyes. Significant changes in GDx parameters were noted in eyes with oblique insertion, which may lead to misinterpretation of a healthy eye as glaucomatous. Hence, GDx parameters in patients noted to have oblique insertion of the temporal arcuate retinal nerve fibre bundle need to be interpreted with caution.*

Key words: *Optic disk, Optic nerve, Prevalence*

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Introduction

Glaucoma is characterised by progressive degeneration of the retinal ganglion cells and their axonal fibres, which eventually leads to nerve fibre layer (NFL) thinning, optic disc cupping, and gradual visual field loss.[1] NFL loss is considered an early sign of glaucoma and is thought to precede the onset of defects on standard white-on-white perimetry.[2] Scanning laser polarimetry is a non-invasive diagnostic method that was developed to assess the retinal nerve fibre layer (RNFL) thickness at a particular location by measuring retardation — that is, the change of the state of polarisation of light reflected from the retina. Because the RNFL is form birefringent, its optical axis is aligned with the retinal nerve fibre bundle orientation, and its retardance is proportional to its thickness.[3,4] The normal pattern shows a thicker NFL in the superior and inferior regions. These areas of higher retardation represent the temporal arcuate retinal nerve fibre bundles. The retardation image is divided into the following 4 segments: 120° segments superior and inferior to the optic disc, a 70° segment nasally, and a 50° segment temporally.

In addition to the RNFL, the cornea also exhibits birefringence properties, which add to the change in polarisation of the incident beam. The polarisation properties of the anterior segment (cornea) are compensated by an opto-electronic device, the 'cornea-polarisation compensator'. The nerve fibre analyser (NFA) GDx uses a fixed corneal compensator (FCC), which has been modified in the latest version with a variable corneal compensator (VCC).

It has been observed that, in some healthy eyes, the temporal arcuate retinal nerve fibre bundle does not strictly lie within the superior and inferior quadrants but is inserted obliquely, partly spreading to the adjacent nasal quadrant. As the superior and inferior NFL thickness is taken into account for all derived GDx parameters, any change in the normal nerve fibre bundle insertion could influence the derived values. Glaucomatous NFL loss preferentially affects the superior and inferior RNFL; any factor that could modify these values would be a potential confounder in diagnosing glaucomatous RNFL loss. This study was designed to document the prevalence of oblique arcuate bundle insertion in healthy eyes and to study its influence on GDx parameters.

Patients and Methods

This study is part of the Chennai Glaucoma Study (CGS), a population-based cross-sectional study of glaucoma among people aged 40 years or older, conducted at a tertiary eye care centre. The study population included for GDx analysis consisted of 463 eyes of 234 healthy South Indian people. Written informed consent was obtained from all participants and the study was performed in accordance with the tenets of the Declaration of Helsinki. The Institutional Review Board approved the study.

All participants underwent a complete ophthalmic examination, including best-corrected visual acuity using the Distance Visual Acuity Test Modified ETDRS chart (Light House Low Vision Products, New York, USA), NFL analysis using the NFA GDx (Version 1.0.16; Laser Diagnostic Technologies, San Diego, USA), frequency doubling perimetry (FDP; Zeiss Humphrey Systems, Dublin, USA), slit lamp examination, applanation tonometry, fundus examination using an indirect ophthalmoscope, and disc evaluation with 78 D at the slit lamp.

The instrument used in this study was the NFA GDx, which has a fixed corneal compensator with a magnitude of 60 nm, and a slow axis oriented downwards 15° nasally. GDx was performed on all participants enrolled in the study by 1 of 2 optometrists experienced in glaucoma diagnostics. The test was done with ambient room illumination and with undilated pupils. One high-quality image was captured per eye. The image had to be well focused, was centred with adequate illumination, and covered all quadrants. The test was repeated up to a maximum of 3 times to obtain a good image. Poor-quality images were excluded. The ellipse was placed on the disc margin and symmetry analysis printouts were taken. Participants with ocular hypertension, narrow angles, glaucoma or glaucoma suspect, large zones of peripapillary atrophy, optic nerve pathology, significant media haze, tilted discs, or split nerve fibre bundles were excluded.

The symmetry analysis printout for each participant was analysed by 2 masked observers for the presence or absence of oblique insertion of the temporal arcuate retinal nerve fibre bundle. An oblique insertion was defined as an arcuate bundle, one-third or more of which crossed the nasal or temporal demarcation lines. If the superior arcuate bundle was oblique, it was classified as superior oblique (Figure 1) and if the inferior arcuate bundle was oblique, it was classified as inferior oblique (Figure 2). For comparison, a control group of 25 eyes of 25 participants with normal insertion of the temporal arcuate retinal nerve fibre bundle was also identified. A normal insertion was defined as one in which the bundle lay entirely within the demarcation lines (Figure 3). In case of a disagreement in classification, the 2 observers re-examined the participant and a consensus was reached. Participants who did not satisfy the criteria for either group were excluded from the analysis.

To confirm an oblique insertion, the actual thickness values of the NFL were examined. The machine provides these as a grid of 16 x 16 squares overlying the captured image of the optic disc and the peripapillary NFL. The thickness value in each square represents the actual thickness in microns of the underlying NFL at that point.[5] Each margin of the bundle was

Figure 1. Oblique insertion of the superior arcuate nerve fibre layer bundle.

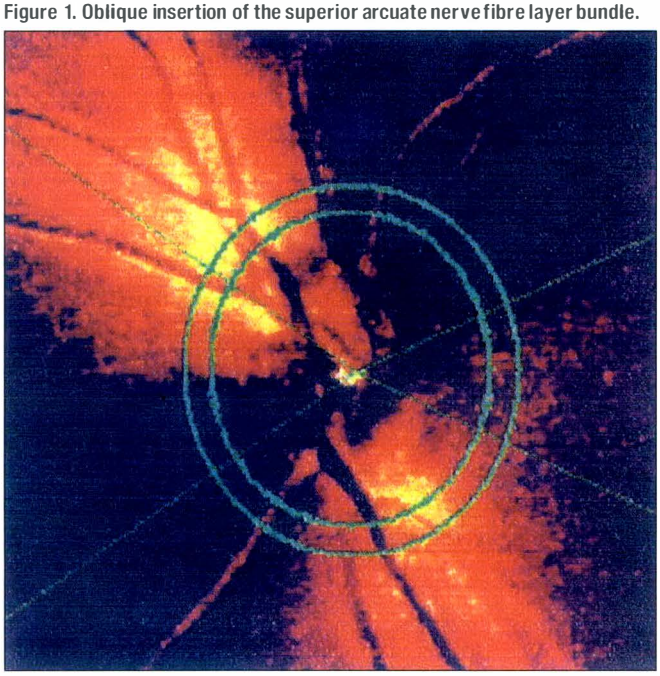


Figure 2. Oblique insertion of the inferior arcuate nerve fibre layer bundle.

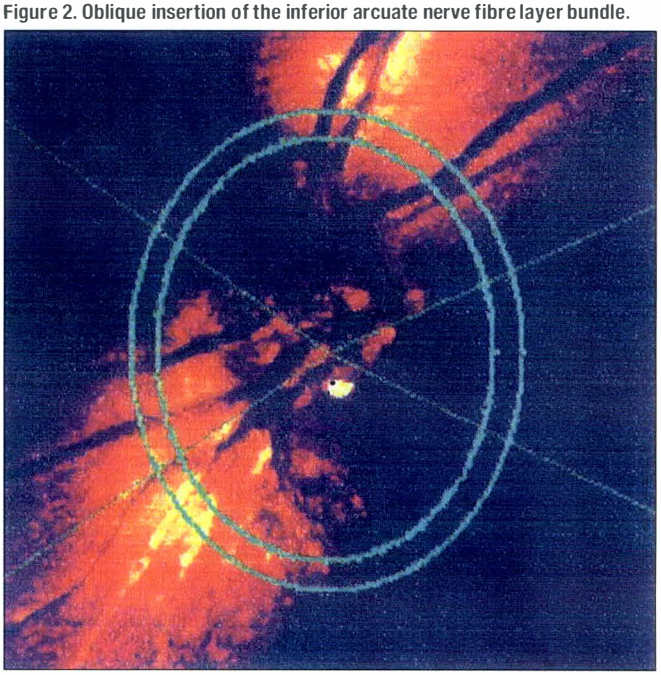
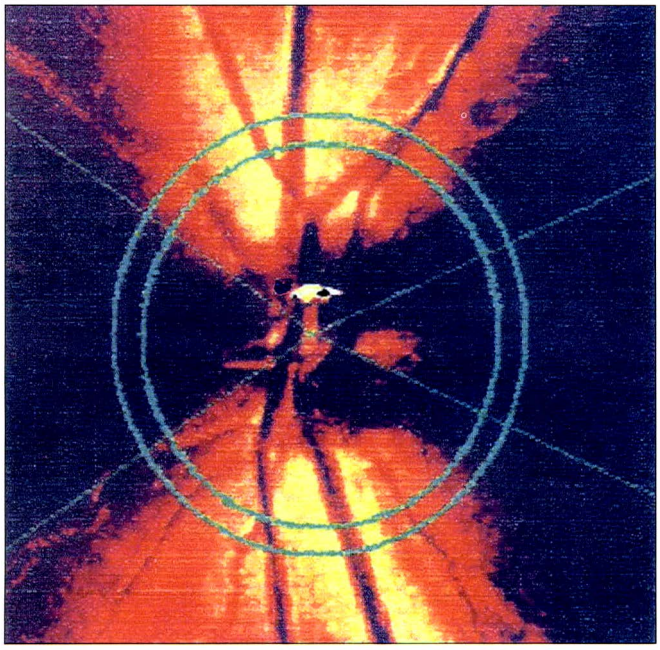


Figure 3. Normal insertion of the temporal arcuate nerve fibre layer bundle.



defined as the border between 2 adjacent squares at the level of the ellipse with a difference in actual thickness values of greater than 5 μm. The nasal and temporal borders of each bundle were defined. The width of the bundle was measured in degrees using a protractor. If more than 30% of the bundle crossed the nasal or temporal demarcation lines, the bundle was confirmed to be oblique.

The 14 parameters in the symmetry analysis printout were compared between the normal group and each of the oblique groups (superior and inferior) using Student's *t* test. In addition, 4 other parameters — namely, the temporal average, nasal average, temporal median, and nasal median — were selected from the numerical printout and similarly analysed.

Results

Of the 463 eyes analysed, 24 eyes were identified to have oblique insertion on the basis of retardation maps. Of these, 23 eyes were confirmed to have oblique insertion on the actual thickness map, a prevalence of 4.97%. All of the eyes with oblique insertion were unilateral — 5 were in the right eye and 18 were in the left eye. Oblique insertion of the superior bundle was noticed in 16 eyes (3.46%), and 7 eyes (1.51%) had oblique insertion of the inferior bundle.

There were 11 men and 12 women with oblique insertion. The control group consisted of 10 men and 15 women. The mean age of the participants with oblique insertion of the temporal arcuate retinal nerve fibre bundle was 45.91 ± 6.63 years (range, 40 to 60 years), and of those with normal insertion was 47.64 ± 6.76 years (range, 40 to 70 years). No significant difference in age was found between the 2 groups. The mean refractive error among participants with oblique insertion (-0.16 D ± 1.19 D) and normal insertion (-0.23 D ± 1.65 D) did not differ significantly.

A statistically significant difference was noted between the 2 groups in most of the GDx parameters (Table 1). Among participants with superior oblique insertion, the superior/nasal ($p = 0.001$) and the superior ratio ($p < 0.001$) parameters were significantly affected. Among participants with inferior insertion, the inferior ratio was significantly affected ($p < 0.001$). The effects of oblique insertion on the GDx parameters compared with normal eyes are shown in Tables 2 and 3.

Discussion

A number of variables can affect GDx measurements. Improvements in corneal compensation have reduced some of the confounders. However, variability in retinal nerve fibre anatomy has received less attention.[6] Colen and Lemij recently highlighted the effect of a split nerve fibre bundle insertion on GDx parameters.[7] The current paper describes another variant of the retinal nerve fibre layer bundle anatomy in a healthy population.

Although the criteria for oblique insertion in this study were arbitrary, the retardation maps seem to accurately depict oblique nerve fibre bundle insertion, as 23 of 24 bundles that were considered to have an oblique insertion on the retardation maps

Table 1. GDx parameter values for eyes with normal nerve fibre bundle insertion compared with eyes with oblique insertion.

Parameter	Normal insertion	Oblique superior insertion	p Value	Oblique inferior insertion	p Value
Number (neural network)	21.24 ± 14.73	20.06 ± 13.51	0.798	20.57 ± 09.78	0.911
Superior maximum	81.95 ± 15.37	91.73 ± 13.51	0.064	110.38 ± 19.95	<0.001
Inferior maximum	78.24 ± 14.90	84.95 ± 16.95	0.200	98.54 ± 13.40	0.003
Symmetry	01.05 ± 00.08	01.10 ± 00.20	0.299	01.12 ± 00.11	0.077
Superior/nasal	02.36 ± 00.28	02.40 ± 00.29	0.001	01.78 ± 00.19	<0.001
Superior ratio	02.48 ± 00.40	02.20 ± 00.29	<0.001	01.82 ± 00.30	<0.001
Inferior ratio	02.36 ± 00.38	01.86 ± 00.27	<0.001	01.63 ± 00.26	<0.001
Average thickness	56.08 ± 09.77	60.06 ± 10.48	0.223	75.57 ± 11.15	<0.001
Ellipse modulation	02.59 ± 00.44	02.92 ± 00.52	0.035	02.82 ± 00.62	0.279
Maximum modulation	01.60 ± 00.34	01.11 ± 00.28	<0.001	00.90 ± 00.23	<0.001
Superior integral	00.20 ± 00.35	00.18 ± 00.04	0.054	00.26 ± 00.06	0.002
Ellipse average	60.59 ± 09.69	63.49 ± 10.61	0.373	78.68 ± 10.87	<0.001
Superior average	70.30 ± 11.57	64.11 ± 11.21	0.099	90.51 ± 14.81	0.001
Temporal average	36.62 ± 07.95	47.59 ± 10.36	<0.001	65.17 ± 18.41	<0.001
Inferior average	71.24 ± 11.87	73.79 ± 14.27	0.539	79.03 ± 09.59	0.122
Nasal average	40.61 ± 07.54	55.18 ± 10.17	<0.001	65.71 ± 08.41	<0.001
Temporal median	33.96 ± 09.06	46.07 ± 09.72	<0.001	62.15 ± 14.34	<0.001
Nasal median	35.33 ± 08.56	45.75 ± 10.54	0.001	62.04 ± 09.42	<0.001

Table 2. GDx parameters showing an increase with oblique nerve fibre layer insertion.

Parameter	Oblique superior insertion	Oblique inferior insertion
Superior maximum	Increase*	Increase†
Inferior maximum	Increase*	Increase†
Symmetry	Increase*	Increase*
Average thickness	Increase*	Increase†
Ellipse modulation	Increase†	Increase*
Ellipse average	Increase*	Increase†
Temporal average	Increase†	Increase†
Inferior average	Increase*	Increase*
Nasal average	Increase†	Increase†
Temporal median	Increase†	Increase†
Nasal median	Increase†	Increase†
Superior integral		Increase†
Superior average		Increase†

* $p > 0.05$.
† $p \leq 0.05$.

Table 3. GDx parameters showing a decrease with oblique nerve fibre layer insertion.

Parameter	Oblique superior insertion	Oblique inferior insertion
Superior/nasal	Decrease*	Decrease*
Superior ratio	Decrease*	Decrease*
Inferior ratio	Decrease*	Decrease*
Maximum modulation	Decrease*	Decrease*
Superior integral	Decrease†	
Superior average	Decrease†	

* $p \leq 0.05$.
† $p > 0.05$.

were confirmed on the thickness map. Using a lesser degree of obliquity on the retardation maps may not give similar results.

The prevalence of oblique nerve fibre layer insertions was 4.97% of 463 eyes that were studied. Obliquity was noted to be unilateral in all participants and a superior oblique insertion was found to be more common (16 of 23 eyes). The retardation values in the nasal quadrant (nasal average and nasal median) were increased in eyes with superior as well as inferior oblique bundles. Since these bundles were rotated nasally, increased thickness in these regions would be expected. However, the temporal retardation values (temporal average and temporal median) also showed an increase among participants with oblique insertion. A similar temporal rotation of the opposite bundle, resulting in an oblique insertion of the temporal arcuate nerve fibre bundle in the corresponding quadrant would explain this finding. The degree of rotation of the opposite bundle, while present, did not meet the criteria for an oblique insertion on the retardation map, possibly because the obliquity was not sufficiently large to be included in the definition.

Among the participants with superior oblique insertion, the superior average parameter showed a decrease in the retardation value compared with normal eyes, perhaps due to a nasal shift of the arcuate bundle with a thicker nasal NFL. This also resulted in a decrease in the superior and inferior ratios.

Among eyes with oblique insertion inferiorly, a statistically significant increase was noted in both superior and inferior thickness values. Eyes with inferior oblique insertion had higher average thickness than eyes with either normal insertion or superior oblique insertion. None of these eyes had hyperopic or crowded discs, which could be associated with an increase in the overall thickness of the NFL. Both the superior and inferior ratios for these eyes decreased, suggesting that while the superior and inferior average thickness was higher than normal, the temporal bundle was still relatively thick compared to normal, indicating a temporal shift of the nerve fibre bundle with a corresponding decrease in the ratio. The prevalence of an oblique NFL may not be large, but does show the inter-individual variability in NFL pattern. Large inter-individual variations in the optic disc are a known factor and can be relatively easily quantified clinically. It is more difficult to detect such differences clinically in the NFL due to absence of equivalent methods of clinical examination.

A recent paper showing the split nerve fibre pattern[7] and this paper showing the oblique NFL insertion suggest that the NFL has more inter-individual variability than previously suspected. Recent reports have suggested that the GDx with the fixed corneal compensator (GDx FCC) that was used in this study is inadequately compensated for corneal polarisation. This has been corrected in later versions of the instrument (GDx VCC), which use a variable corneal compensator. However, using the GDx VCC to replicate this study is difficult, as the GDx VCC does not provide the thickness map that was used to confirm oblique insertion in this study and the colour codes for the retardation maps are different for the 2 instruments. It is possible that part of this obliquity may be related to inadequate corneal compensation. However, when the GDx NFA was used to perform macular scans in a subset of the participants with an oblique insertion, it was found that 8/14 (57%) were adequately compensated on the macular scan. As 57% of this subset had adequately compensated scans, it is unlikely that the obliquity is secondary to corneal compensation issues alone.

This study has been performed only for normal eyes. GDx parameters show differences in values between eyes with oblique

insertion and normal insertion of the temporal arcuate retinal nerve fibre bundle at the optic disc. GDx parameters related to the superior and inferior quadrants are believed to be significantly affected in glaucoma. Changes in these parameters have been noted in eyes with oblique insertion in this study. This may lead to misinterpreting a normal eye as being glaucomatous. Hence, GDx parameters in eyes noted to have oblique insertion of the temporal arcuate retinal nerve fibre bundle need to be interpreted with caution.

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References

1. Ritch R, Sheilds B, Krupin T. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas. 2nd ed. St Louis: Mosby-Year Book; 1996:1449-1461.
2. Tuulonen A, Lehtola J, Airaksinen PJ. Nerve fiber layer defects with normal visual fields. Do normal optic disc and normal visual field indicate absence of glaucomatous abnormality? Ophthalmology 1993;100: 587-597.
3. Weinreb RN, Shakiba S, Zangwill L. Scanning laser polarimetry to measure the nerve fiber layer of normal and glaucomatous eyes. Am J Ophthalmol 1995;119: 627-636.
4. Zhou QY, Weinreb RN. Individualized compensation of anterior segment birefringence during scanning laser polarimetry. Invest Ophthalmol Vis Sci 2002;43:2221-2228.
5. Nerve Fiber Analyzer System. GDx™ System Manual. Laser Diagnostic Technologies Inc; 1997.
6. Weinreb RN, Bowd C, Zangwill L. Scanning laser polarimetry in monkey eyes using variable corneal polarization compensation. J Glaucoma 2002;11:378-384.
7. Colen TP, Lemij HG. Prevalence of split nerve fiber bundles in healthy eyes images with scanning laser polarimetry. Ophthalmol 2002;108:151-156.

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Comparison of Subscleral Partial Thickness Sclerectomy plus Trabeculotomy with Trabeculectomy for Primary Open Angle Glaucoma

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Aim: *To compare the success rate and complications of subscleral partial thickness sclerectomy plus trabeculotomy with those of trabeculectomy alone for primary open angle glaucoma.*

Patients and Methods: *Sixty seven eyes of 67 patients with primary open angle glaucoma were enrolled in this randomised controlled trial. Thirty four eyes of 34 patients underwent subscleral partial thickness sclerectomy plus trabeculotomy with mitomycin C and 33 eyes of 33 patients underwent modified Cairn's trabeculectomy with mitomycin C. A complete ophthalmic examination was performed before surgery and on postoperative days 1, 3, 5, and 7, and after 2, 3, and 4 weeks, and 3, 6, 12, 18, and 24 months.*

Results: *The cumulative probability of complete success (intraocular pressure <21 mm Hg without medication) after 2 years, using Kaplan-Meier survival analysis, was 76% in the eyes that underwent trabeculectomy alone compared with 52% in the eyes that underwent subscleral partial thickness sclerectomy plus trabeculotomy (log-rank test, p = 0.07). Two eyes in the trabeculectomy-alone group had flat anterior chambers with corneolenticular touch and required anterior chamber reformation. Hyphaema and development and progression of cataract were observed more frequently in patients receiving trabeculectomy than in those receiving subscleral partial thickness sclerectomy with trabeculotomy.*

Conclusion: *Subscleral partial thickness sclerectomy plus trabeculotomy with mitomycin C offers an alternative to standard trabeculectomy with mitomycin C.*

Key Words: Glaucoma, open angle, Trabeculectomy

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Introduction

Trabeculectomy is generally considered to be the gold standard of surgery to reduce intraocular pressure (IOP) in eyes with primary open angle glaucoma (POAG). However, this technique is associated with complications, including anterior uveitis, excessive filtration leading to shallow or flat anterior chamber, hypotony, hypotonic maculopathy, choroidal detachment, and endophthalmitis.[1-4] Non-penetrating filtering surgery has been attempted to decrease the incidence of complications and achieve control of IOP in these eyes.

Epstein noticed oozing of aqueous humour from the paralimbal area during dissection of deep-seated pterygium.[5] This author suggested that paralimbal deep sclerectomy may be performed to lower the IOP in patients with glaucoma. Subsequently, Epstein described the technique of paralimbal deep sclerectomy overlying Schlemm's canal, with a 180° circumference, while avoiding entry into the anterior chamber. The technique resulted in short-term success because of scarring of the conjunctiva overlying Schlemm's canal and episcleral tissue. Krasnov reported a similar operation during the same period and named the procedure sinusotomy.[6] The non-penetrating filtration surgery reduced the IOP by a mean of 50%; the longevity of successful filtration ranged from 19.0 to 37.0 months and the mean duration was 29.9 months.[7] To prolong the duration of filtration, collagen or hyaluronic acid implants were used under the scleral flap.[8-11] Mizoguchi et al evaluated the results of trabeculotomy with sinusotomy in 40 eyes with POAG and reported a 74% cumulative success rate for IOP control (≤19 mm Hg) after 4 years.[12] However, there has been no prospective randomised study to compare and evaluate partial thickness sclerectomy combined with trabeculotomy versus standard trabeculectomy in eyes with POAG. The purpose of this randomised controlled trial was to clinically analyse whether partial thickness sclerectomy combined with trabeculotomy with intraoperative use of mitomycin C (MMC) can improve the success rate of the combined surgical procedure without producing the complications associated with trabeculectomy with MMC.

Patients and Methods

Sixty seven eyes of 67 consecutive patients with POAG from the Glaucoma Clinic at the Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India, were enrolled in the study. All patients were Asian.

Inclusion criteria were IOP not controlled (>21 mm Hg) with maximally tolerated medical therapy, presence of glaucomatous visual field loss, and cupping of more than 0.5:1 in the presence of open angles at gonioscopy. Exclusion criteria were corneal

opacity that prevented reliable IOP measurement by Goldmann applanation tonometry, secondary glaucomas, history of intraocular surgery, and inability to maintain a regular follow-up schedule.

Informed consent was obtained from all patients after the risks and benefits of the surgery had been explained. Approval of the Ethics Committee of the All India Institute of Medical Sciences was obtained before commencing the study.

A detailed clinical history was recorded for all patients. The ophthalmic examinations performed at the screening visit and 1 day prior to surgery included best-corrected Snellen visual acuity, slit lamp biomicroscopy, direct ophthalmoscopy, optic disc evaluation with a lens of +90 D on a slit lamp, Goldmann applanation tonometry, gonioscopy, and perimetry with a Humphrey 30-2 programme (Humphrey field analyzer; Zeiss, San Leandro, USA). Antiglaucoma medications were continued prior to surgery. After surgery, the same examinations, except for gonioscopy, were performed on postoperative days 1, 3, 5, and 7, and after 2, 3, and 4 weeks, and 3, 6, 12 ,18, and 24 months. The visual field examination was repeated after 6, 12, 18, and 24 months. If a patient did not attend for a scheduled visit, the mean IOP readings of the previous and subsequent visits were used for analysis. Anterior chamber depth was measured preoperatively and again from the fifth postoperative day using ultrasonography (Nidek Echoscan US – 3300; Nidek, Tokyo, Japan).The optometrist performing the investigations was blinded to the surgery performed.

Complications were defined as hyphaema when red blood cells were observed in the anterior chamber, and as hypotony when the IOP decreased to below 6 mm Hg. The anterior chamber depth was graded as shallow in the presence of iridocorneal touch in the periphery (grade 1) or mid-periphery (grade 2) and flat if a lens corneal touch was observed (grade 3). Chronic anterior chamber inflammation was present when cells 1+ or flare 2+ were seen by biomicroscopic examination for more than 2 postoperative weeks. Choroidal detachment was considered present when detected by indirect ophthalmoscopy. Cataract was noted to be a direct result of surgery and defined as 'surgery-related cataract' when there was no previous lenticular opacity and the condition was associated with a rapid decrease in visual acuity of more than 2 Snellen lines (within 1 month of surgery). When the cataract was associated with a slowly progressive decrease in visual acuity of more than 2 Snellen lines, it was defined as 'cataract progression'.

Patients were randomised preoperatively (by computer-generated randomisation) to receive either subscleral partial thickness sclerectomy plus trabeculotomy with MMC (SST) or modified Cairn's trabeculectomy with MMC (TE). All surgical procedures were performed under peribulbar anesthaesia by the same surgeon.

Subscleral Partial Thickness Sclerectomy with Trabeculotomy

After a limbus-based conjunctival flap had been made, 0.2 mL of MMC 0.2 mg/mL in a 4- x 6-mm sponge was applied under Tenon's capsule for 2 minutes and thoroughly washed off. A triangular scleral thickness superficial flap of 4 x 4 mm was prepared. An inner scleral flap of 3.5 x 3.5 mm from the scleral bed extending for approximately 1 mm inside the limbus was dissected and pulled up while the floor of Schlemm's canal and Descemet's membrane were depressed with the tip of the cellulose sponge until the dark-coloured uveal tissue could be seen. The membrane was cleaved from the cornea for a distance of 1 mm and the inner scleral flap was excised. The cut end of Schlemm's canal was identified by oozing of the aqueous humour on the 2 sides of the triangular corneoscleral bed. Harm's trabeculotome was passed into the lumen of Schlemm's canal and was rotated towards the pupil to rupture the inner wall of Schlemm's canal on both sides as previously described.[13] The superficial scleral flap was approximated with 3 interrupted 10-0 nylon sutures. The cut edges of Tenon's capsule and the conjunctival flap were approximated by a continuous 8-0 vicryl suture.

Trabeculectomy

A limbus-based conjunctival flap was prepared and 0.2 mL of MMC 0.2 mg/mL in a 4- x 6-mm sponge was applied under Tenon's capsule for 2 minutes and thoroughly washed off. After a triangular superficial scleral flap of 4 x 4 mm had been dissected, a 2- x 2-mm corneoscleral bed was dissected to include the trabecular meshwork. A peripheral iridectomy was performed. The superficial scleral flap was closed with 3 interrupted 10-0 nylon sutures. The sutures were adjusted to allow minimal leakage during reformation of the anterior chamber with balanced salt solution. The edges of Tenon's capsule and the conjunctiva were approximated with 8-0 vicryl sutures. Subconjunctival steroid and antibiotics were administered to all patients. Postoperatively, each eye received topical steroid and antibiotic eyedrops 4 times a day. The steroid dose was gradually tapered depending on the inflammatory response of the eye and stopped after 4 weeks. All antiglaucoma treatment was stopped in the operated eye after surgery.

Statistical Analysis

The difference between the paired samples between groups were analysed with the Wilcoxon signed rank test. Kaplan-Meier analysis for IOP survival was done to ascertain the cumulative probability of complete success for achieving an IOP of less than 21 mm Hg and less than 14 mm Hg

without antiglaucoma therapy, and the log-rank test was used to compare the 2 groups. Qualified success was defined as an IOP of less than 21 mm Hg with topical antiglaucoma therapy. The Statistical Package for the Social Sciences version 10.0 was used for statistical analyses.

Results

Thirty three eyes underwent TE and 34 eyes underwent SST. There were 40 men and 27 women. Table 1 shows the clinical profiles of the 2 groups. The mean (± standard deviation) follow-up duration was 20.0 ± 2.4 months for the SST group and 20.2 ± 2.1 months for the TE group. All patients in both groups were followed up for a minimum of 12 months, and 23 patients in the TE group and 20 in the SST group were followed up for 2 years.

The mean preoperative IOP was 29.6 ± 5.6 mm Hg in the TE group and 31.2 ± 6.8 mm Hg in the SST group. At the 1-year follow-up visit, the IOP decreased to 13.1 ± 2.7 mm Hg (57.3%) in the TE group and 15.8 ± 4.3 mm Hg (51.4%) in the SST group (Figure 1). After 1 year, complete success was achieved for 24 eyes (71%) and qualified success for 8 eyes (23%) after SST compared with complete success for 32 eyes (97%) and qualified success for 1 eye (3%) after TE. The 2 eyes in the SST group in which the IOP was not controlled with maximum tolerable antiglaucoma therapy (designated as failure of surgery) underwent trabeculectomy after 6 months. Figures 2 and 3 show the Kaplan-Meier curves for complete success for IOP of less than 21 mm Hg and less than 14 mm Hg for a 2-year follow-up period. In each case, the difference between the 2 groups using the log-rank test was not significant. For example, the cumulative probability of complete success (<21 mm Hg) was 76% for the TE group and 52% for the SST group ($p = 0.07$).

The mean number of medications declined from 1.7 ± 0.5 to 0.8 ± 0.2 in the SST group and from 1.8 ± 0.9 to 0.5 ± 0.1 in the TE group ($p = 0.02$). Two eyes in the TE group had a flat anterior chamber that required reformation with 2% hydroxypropyl methylcellulose (HPMC).

Anterior chamber reaction during the first week after surgery was present in all eyes in the TE group, but in none of the eyes in the SST group. The cells and flare subsided in all eyes after the first week of treatment with topical steroids. None of the eyes had chronic anterior chamber inflammation persisting beyond 1 week. Other complications such as hyphaema and development and progression of cataract were observed more

Figure 1. Intraocular pressure during 1 year of follow-up.

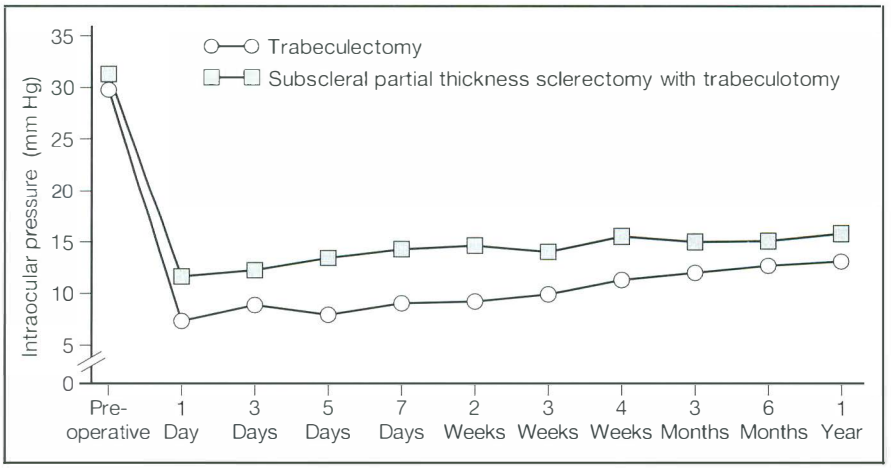

Figure 2. Cumulative probability of complete success (IOP <21 mm Hg without antiglaucoma medication) using Kaplan-Meier life-table analysis.

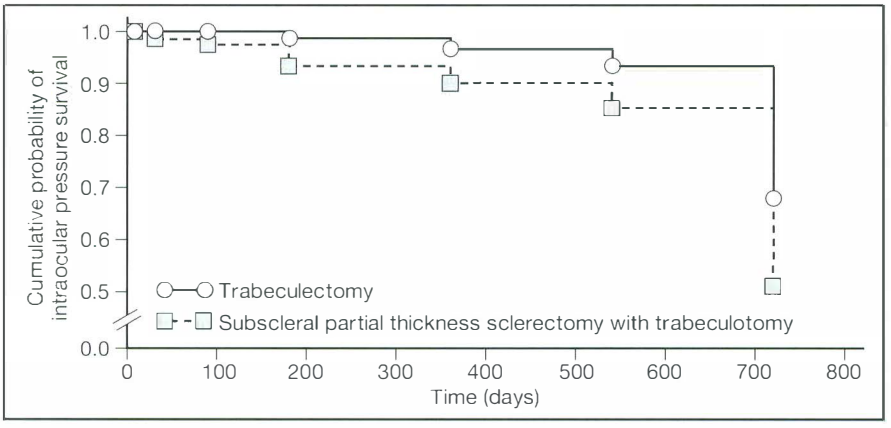

Table 1. Patients' characteristics (mean ± standard deviation).

Characteristic	Subscleral partial thickness sclerectomy plus trabeculotomy (n = 34)	Trabeculectomy (n = 33)	p Value
Sex			0.1
Male	22	18	
Female	12	15	
Age (years)	44.1 ± 2.8	46.6 ± 3.5	0.2
Follow-up (months)	20.0 ± 2.4	20.2 ± 2.1	0.6
Preoperative intraocular pressure (mm Hg)	31.2 ± 6.8	29.6 ± 5.6	0.06
Mean number of preoperative topical medications	1.7 ± 0.5	1.8 ± 0.9	0.07
Duration of preoperative topical medication (months)	6.2 ± 2.3	6.4 ± 2.3	0.4

Figure 3. Cumulative probability of complete success (IOP <14 mm Hg without antiglaucoma medication) using Kaplan-Meier life-table analysis.

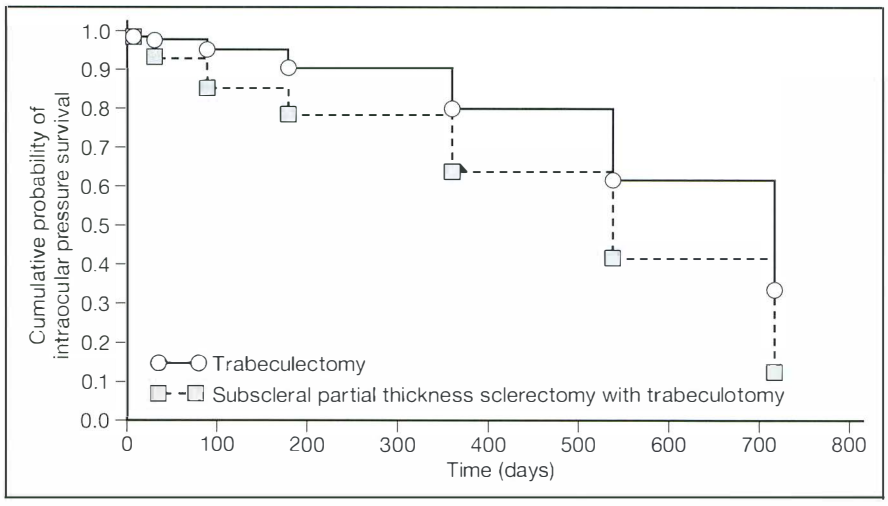

Table 2. Postoperative complications.

Complication	Subscleral partial thickness sclerectomy plus trabeculotomy (%) [n = 34]	Trabeculectomy (%) [n = 33]	p Value
Hyphaema	2 (6)	5 (15)	0.4
Hypotony	0	3 (9)	0.22
Shallow anterior chamber			
Total	0	10 (30)	0.0017
Grade 1	0	5 (15)	
Grade 2	0	3 (9)	
Grade 3	0	2 (6)	
Chronic anterior chamber inflammation	0	0	
Failed surgery	2 (6)	0	0.44
Cataract			
Total	1 (3)	6 (18)	0.1
Development	0	2 (6)	
Progression	1 (3)	4 (12)	

frequently in the TE group than in the SST group (Table 2).

At the last follow-up, best-corrected visual acuity decline of more than 2 Snellen lines occurred in 6 eyes in the TE group; this was due to a flat anterior chamber and subsequent surgery-related cataract development in 2 eyes and cataract progression in the other 4 eyes. Hypotonic maculopathy was not observed in any of the eyes until the last follow-up. In the SST group, visual acuity decline of greater than 2 Snellen lines occurred in 1 eye because of progression of cataract. Accidental perforation was not encountered during deep sclerectomy, and none of the eyes in the SST group had haemorrhagic Descemet's detachment.

Visual fields and optic discs did not show definite glaucomatous progression in any of the eyes during the 2-year follow-up period.

Discussion

It is increasingly understood that an IOP of less than 21 mm Hg and stable perimetry results are not the best measures of success for treating patients with glaucoma. Preservation of functional vision with minimal disturbance to quality of life are the ideal measures. Owing to the potential vision threatening complications of trabeculectomy with or without antimetabolites, many surgeons prefer to delay surgery, especially for patients with a grossly reduced field of vision. If the safety margin of glaucoma surgery could be increased without sacrificing efficacy, surgical intervention for glaucoma may be considered earlier. Recently, there has emerged an interest in performing non-perforating filtering surgery such as non-penetrating trabeculectomy,[14] viscocanalostomy,[15] deep sclerectomy with wick drains and collagen implants,[9,10,11,16] trabecular vacuuming,[17] and ab interno goniotrabeculectomy[18] in an attempt to decrease the postoperative complications of standard filtering surgery. The advantages of these techniques are avoidance of prolonged hypotony, reduced postoperative inflammation, minimal need for postoperative medications, and rapid visual recovery. However, preliminary results show that IOP reductions with these procedures are lower than with trabeculectomy.[19] Using collagen implants, Shaarawy et al reported 95% qualified success and 62% complete success rates after 5 years in a prospective study of 105 eyes that underwent deep sclerectomy.[20] Collagen and hyaluronic acid implants are costlier and therefore not feasible to use for all patients undergoing non-penetrating filtering surgery.

An advantage of combining deep sclerectomy with trabeculotomy and using intraoperative MMC was considered to improve the results in relation to IOP control. The mechanisms proposed for the drainage of aqueous after deep sclerectomy include episcleral drainage via Schlemm's canal, the intrascleral bleb, and the subconjunctival bleb, and partly through the subchoroidal passage.[21]

Several researchers have used MMC during trabeculectomy and reported improved success rates compared with trabeculectomy without MMC.[22-25] Nakaizumi et al[26] and Kozobolis et al[27] also reported greater success with the use of MMC for deep sclerectomy. In the patients with POAG reported in this study, the complete or quali-

fied success rate for IOP control after 12 months for TE (100%) was comparable to that for SST (94%), although the absolute success rate for the former procedure (97%) was greater than for the latter procedure (71%). These results are better than those reported by Ambresin et al, who performed deep sclerectomy with collagen implants in 1 eye and compared the results with the contralateral eye, which underwent trabeculectomy.[28] However, these authors also included patients with secondary open angle glaucoma in their study.

In this study, 2 eyes undergoing SST had uncontrolled IOPs, even with maximally tolerated antiglaucoma therapy; the 2 eyes subsequently underwent trabeculectomy. More eyes had shallow anterior chambers after TE than SST. Two eyes developed corneolenticular touch after TE and required reformation of the anterior chamber with 2% HPMC. At the final follow-up visit, visual acuity decreased in 6 eyes by more than 2 lines after trabeculectomy because of cataract, whereas only 1 eye had a decrease of more than 2 lines after SST. Similar results have been reported by other authors.[29] Complications such as anterior chamber reaction, hyphaema, and hypotony were observed more frequently after trabeculectomy.

Although the number of eyes was limited, this preliminary study shows that application of MMC during SST is a promising alternative to conventional trabeculectomy with MMC. A thorough evaluation in a larger series of eyes with a longer follow-up may substantiate these results.

References

1. Watson PG, Jakeman C, Ozturk M, Barnett MF, Barnett F, Khaw KT. Complications of trabeculectomy (a 20-year follow-up). Eye 1990;4:425-438.
2. Kao SF, Lichter PR, Musch DC. Anterior chamber depth following filtration surgery. Ophthalmic Surg 1989;20:332-336.
3. Brubaker RF, Pederson JE. Ciliochoroidal detachment. Surv Ophthalmol 1983;27: 281-289.
4. Solomon A, Ticho U, Frucht–Pery J. Late onset bleb associated endophthalmitis following glaucoma filtering surgery with or without antifibrotic agents. J Ocul Pharmacol Ther 1999;15:283-293.
5. Epstein E. Fibrosing response to aqueous: its relationship to glaucoma. Br J Ophthalmol 1959;43:641-647.
6. Krasnov MM. Externalisation of Schlemm's canal (sinusotomy) in glaucoma. Br J Ophthalmol 1968;57:157-161.
7. Dahan E, Drusedau MUH. Nonpenetrating filtration surgery for glaucoma: control by surgery only. J Cataract Refract Surg 2000; 26:695-701.
8. Sanchez E, Schnyder CC, Sickenberg M, Chiou AG, Hediguer SE, Mermoud A. Deep sclerectomy: results with and without collagen implants. Int Opthalmol 1996-97; 20:157-162.
9. Karlen ME, Sanchez E, Schnyder CC, Sickenberg M, Mermoud A. Deep sclerectomy with collagen implant: medium term results. Br J Ophthalmol 1999;83:6-11.
10. Spinelli D, Curatola MR, Faroni E. Comparison between deep sclerectomy with reticulated hyaluronic acid implant and trabeculectomy in glaucoma surgery. Acta Opthalmol Scand Suppl 2000;2322:60-62.
11. Sourdille P, Santiago PY, Villain F, et al. Reticulated hyaluronic acid implant in nonperforating trabecular surgery. J Cataract Refract Surg 1999;25:332-339.
12. Mizoguchi T, Nagata M, Matsumura M, Kuroda S, Terauchi H, Tanihara H. Surgical effects of combined trabeculotomy and sinusotomy compared to trabeculotomy alone. Acta Ophthalmol Scand 2000;78: 191-195.
13. Tanihara H, Negi A, Akimoto M, et al. Surgical effects of trabeculotomy ab externo on adult eyes with primary open angle glaucoma and pseudoexfoliation syndrome. Arch Ophthalmol 1993;111: 1653-1661.
14. Zimmerman TJ, Kooner KS, Ford VJ, et al. Trabeculectomy vs non-penetrating trabeculectomy: a retrospective study of two procedures in phakic patients with glaucoma. Ophthalmic Surg 1984;15: 734-740.
15. Stegmann R, Pienaar M, Miller D. Viscocanalostomy for open angle glaucoma in black African patients . J Cataract Refract Surg 1999;25:316-322.
16. Welsh NH, DeLange J, Wasserman P, Ziemba SL. The deroofing of Schlemm's canal in patients with open angle glaucoma through placement of collagen drainage device. Ophthalmic Surg Lasers 1998;29: 216-226.
17. Jacobi PC, Dietlein TS, Krieglstein GK. Comparative study of trabecular aspiration versus trabeculectomy in glaucoma triple procedure to treat pseudoexfoliation glaucoma. Arch Opthalmol 1999;117: 1311-1318.
18. Quaranta L, Hitchings RA, Quaranta CA. Ab-interno goniotrabeculotomy versus mitomycin C for adult open-angle glaucoma: a 2-year randomized clinical trial. Ophthalmology 1999;106:1357-1362.
19. Chiselita D. Nonpenetrating deep sclerectomy versus trabeculectomy in primary open angle glaucoma surgery. Eye 2001;15:197-201.
20. Shaarawy T, Karlen M, Schnyder C, Achache F, Sanchez E, Mermoud A. Five-year results of deep sclerectomy with collagen implant. J Cataract Refract Surg 2001;27:1770-1778.
21. Mermoud A, Shaarawy T. Nonpenetrating glaucoma surgery. London: Martin Dunitz Ltd; 2001:60-61
22. Diestelhorst M, Khalili MA, Krieglstein GK. Trabeculectomy: a retrospective follow-up of 700 eyes. Int Ophthalmol 1999;22: 211-220.
23. Agarwal HC, Saigal D, Sihota R. Assessing the role of subconjunctival versus intrascleral application of mitomycin C in high-risk trabeculectomies. Indian J Ophthalmol 2001;49:91-95.
24. Loo SC, Chew PTK. A major review of antimetabolites in glaucoma therapy. Ophthalmologica 1999;213:234-245.
25. Sihota R, Sood NN, Agarwal HC. Mitomycin C drops in the postoperative pharmacological modulation of trabeculectomies. Ann Ophthalmol 1997;29:362-366.
26. Nakaizumi T, Tsuji H, Araie M. Sinusotomy with intraoperative mitomycin-C administration in selected eyes with advanced glaucomatous damage. Nippon Gauka Gakkai Zasshi 2000;104:154-159.
27. Kozobolis VP, Christodoulakis EV, Tzanakis N, Zacharopoulos I, Pallikaris IG. Primary deep sclerectomy vs primary deep sclerectomy with the use of mitomycin C in POAG. J Glaucoma 2002;11:287-293.
28. Ambresin A, Shaarawy T, Mermoud A. Deep sclerectomy with collagen implant in one eye compared with trabeculectomy in the other eye of the same patient. J Glaucoma 2002;11:214-220.
29. Henchoz L, Schnyder C, Shaarawy T, et al. Surgery induced cataract and cataract progression following deep sclerectomy with collagen implant compared to trabeculectomy. Ophthalmology 2000;107: 205-210.

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Influence of Age, Race, Sex, and Socioeconomic Status on False-negative Rates of Visual Fields in Glaucoma

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***Aim**: An increased frequency of false-negative rates for visual fields in glaucoma has been associated with worse visual field status. This study examines whether this finding might also vary according to age, race, sex, or socioeconomic status — demographic factors unrelated to glaucoma that may affect visual field performance.*

***Patients and Methods**: This study was a retrospective observational case series. Of 1200 charts of patients undergoing visual field testing, 297 were included. The inclusion criteria were unilateral glaucomatous field loss, prior experience with visual field testing, and a visual field defect in 1 eye on at least 2 examinations. Data were analysed using the Wilcoxon signed rank test, Wilcoxon rank sum test, and Kruskall-Wallis test.*

***Results**: Of 297 patients with unilateral glaucomatous field loss, there were 175 men and 122 women. 123 patients were Caucasian and 128 were black. Seventy four patients (24.92%) were enrolled from a private clinic, 90 (30.30%) from a Veterans Administration hospital, and 133 (44.78%) from a county hospital. The mean false-negative rate in affected eyes was 12.56, while that in unaffected eyes was 4.19. The intrapatient intereye difference in false-negative rates was 8.43 ($p < 0.001$). However, intrapatient intereye differences in false-negative rates did not vary significantly by patients' age, race, sex, or socioeconomic status.*

***Conclusions**: High false-negative rates are closely associated with worsening glaucomatous visual field defects, but age, race, sex, and socioeconomic status do not appear to significantly influence false-negative rates.*

Key Words: *Demography, False negative reactions, Glaucoma, Visual fields*

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Introduction

It has been shown that false-negative rates (FNRs) for visual fields increase with severity of visual field loss.[1-3] FNRs indicate a failure to respond to a stimulus that is 9 dB brighter than a stimulus previously seen at the same location. A patient may become fatigued during visual field testing and fail to respond to a stimulus that has previously been seen.[4-6] FNRs may also signify that a patient is unable to see the brighter stimulus on second presentation owing to a widely damaged visual field.[1-3] Therefore, FNRs in advanced glaucoma do not necessarily mean that the test is unreliable. However, given the demands of automated visual field testing, it is unclear whether individuals of lower socioeconomic status or with certain demographic characteristics may find the test more difficult to perform than other individuals, and thus have higher FNRs that might confound the test results. There is an impression among some practitioners that patients of lower socioeconomic status may have unreliable results. However, this may not be a reflection of reliability as much as severity of disease, because it has been shown that individuals of lower socioeconomic status present later and with more severe disease.[7]

This study examines whether socioeconomic status (represented by the general clinic population) is related to decreased reliability in visual field test performance after adjusting for severity of visual field loss. The study also aimed to determine whether other demographic factors of age, race, and sex affect reliability indices, specifically FNRs, for automated perimetry. This is the first study to examine whether reliability indices are affected by external factors.

Patients and Methods

1200 consecutive charts of patients undergoing visual field testing at 3 centres between April 1996 and December 2000 were retrospectively reviewed. The study protocol was approved by the institutional review board or ethics committees of the 3 clinics.

Patients included in the study were known to have glaucoma, as well as unilateral glaucomatous field loss, prior experience with visual field testing, and a visual field defect in 1 eye on at least 2 examinations. Eligible visual field defects were defined as having at least 2 adjacent points of -5 dB or less. Exclusion criteria included visual field defects from retinal, macular, or neurological diseases. Diagnosis of glaucoma was based on signs of

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a glaucomatous optic disc such as vertically oval cupping, disparity of cups in both eyes, neural rim thinning or notching, saucerisation, nasalisation of vessels, or total cupping, and on the corresponding visual field defects such as nasal step, or paracentral or arcuate scotoma, with or without elevated intraocular pressure (IOP). Of the 1200 patients reviewed, 297 were eligible for the study.

The 3 centres included a private clinic, a Veterans Administration (VA) hospital, and a county hospital. The private clinic (clinic A) is attached to the University of Texas Southwestern Medical Center at Dallas, USA. The patients attending this clinic have health insurance or are self-payers. For the purpose of this study, patients attending clinic A were considered to belong to a higher socioeconomic group, with a median annual income of US$50,000 per household and no upper limit. Clinic B is located at the local VA hospital. According to the Public Affairs office, the average household income for these patients is US$23,500 per year. The patients from the VA hospital were arbitrarily considered to be in the middle socioeconomic group. Clinic C represents the county hospital (Parkland Memorial Health and Hospital System in Dallas, USA), which provides health care to residents of Dallas and Tarrant Counties. This clinic is mainly staffed by the Medical Center's ophthalmology residents under full-time supervision. The health care cost for each patient is based on the patient's income and ability to pay. The average annual income is US$12,000 and these patients were considered to be in the lower socioeconomic group.

All patients were tested using the Humphrey SITA Standard white-on-white 30-2 programme (Humphrey Instruments, San Leandro, USA); right eyes were routinely tested first. The FNR was calculated from the percentage value on the printout, which represents how frequently a patient misses a stimulus brighter than the one previously seen in the same location. The intrapatient intereye difference in FNR (ΔFNR) was calculated by taking the difference between the FNR in affected eyes and the FNR in the contralateral eye with normal visual field testing. The amount of field loss was estimated by 2 methods. Firstly, if the defect was mainly confined to 1 quadrant, the damage was considered mild, field defects in 2 quadrants were considered moderate, and scotomas in 3 or more quadrants were considered severe. Secondly, a global estimate of the extent of field loss was estimated by mean deviation (MD), which has been shown to correlate well with visual field scores from the Collaborative Initial Glaucoma Treatment Study (CIGTS).[8]

Data analyses were performed using the Statistical Analysis System (SAS Institute Inc, Cary, USA). The distributions of reliability measures and of MD values were not normal. Therefore, non-parametric tests were used for these measures. ΔFNRs were calculated and compared using the Wilcoxon signed rank test. The relationship between ΔFNRs and MD values and demographic characteristics were tested by the Wilcoxon rank sum and Kruskall-Wallis tests for univariable analyses and with analysis of variance on the ranks of the outcome measures for multivariable analyses. A p value of 0.05 or less was considered statistically significant. Similar analyses were also performed for false-positive rate (FPR) and fixation loss rate (FLR).

Results

Demographics

The patients' demographics are shown in Table 1. Age was similar among the 3 groups; the mean (± standard deviation)

Table 1. Patients' demographics.

Variable (n = 297)	Number (%)	Age ± standard deviation (years)
Age (years)		63.74 ± 12.69
Range		15 - 88
Sex		
Male	175 (58.92)	64.53 ± 13.29
Female	122 (41.08)	62.61 ± 11.74
Race		
Caucasian	123 (41.41)	67.73 ± 11.98
Black	128 (43.10)	61.27 ± 13.37
Hispanic	36 (12.12)	59.69 ± 9.71
Asian	10 (3.37)	60.90 ± 9.09
Socioeconomic status		
Upper (clinic A)	74 (24.92)	61.39 ± 12.43
Middle (clinic B)	90 (30.30)	68.68 ± 11.63
Lower (clinic C)	133 (44.78)	61.71 ± 12.67
Affected eye		
Right	141 (47.47)	
Left	156 (52.53)	
Refraction		
Hyperopia	91 (31.93)	
Myopia	121 (42.46)	
Plano	73 (25.61)	
Severity of visual field loss		
Mild	105 (33.35)	
Moderate	99 (33.33)	
Severe	93 (31.31)	
Type of glaucoma		
Open angle	271 (91.86)	
Angle closure	24 (8.11)	
Number of medications		
0	34 (12.06)	
1-2	190 (67.37)	
>2	58 (20.57)	

age was 63.74 ± 12.69 years. The subtypes of glaucoma were distributed evenly among the clinics.

False-negative Rate

The mean FNR in affected eyes was 12.56 versus 4.19 in unaffected eyes (Table 2). The ΔFNR was 8.43 ($p < 0.001$). The FNR was higher in affected eyes in more than half of the patients (51.43%; 151/288, with 9 patients excluded owing to lack of information). The ΔFNRs exceeded 5 in both eyes in 51 patients. In these patients, the ΔFNR was 3.09. Comparison of ΔFNR among the various races was not significant, but the mean FNRs in affected eyes were higher than in non-affected eyes, with ΔFNR ranging from 7.26 to 9.66 (Table 2).

The mean FNRs in affected eyes of men and women were also higher than in unaffected eyes. The change in FNR between the sexes was not significantly different. Patients from the higher income group (clinic A) had a ΔFNR of 5.21, which was lower than the values for the patients from the middle (clinic B) and lower (clinic C) income groups of 10.24 and 9.06, respectively. The ΔFNRs among the 3 groups were not significantly different.

False-positive Rate

The mean FPR was 3.39 (range, 0.00 to 37.50) in glaucomatous eyes and 3.83 (range, 0.00 to 44.44) in healthy eyes. The average difference in mean FPR response was -0.44. Comparisons of the change in FPR among races and sexes were not significant. Comparison of the change in FPR between clinics showed a statistically significant difference ($p < 0.001$).

Fixation Loss Rate

The FLR was 9.67 (range, 0.00 to 95.45) in glaucomatous eyes, compared with 12.65 (range, 0.00 to 100.00) in unaffected eyes. Of those eyes with FLRs of more than 20, forty two eyes were glaucomatous (FNR = 14.03), and 60 eyes were unaffected (FNR = 5.30).

Visual Field

The relationship between ΔFNR and the degree of visual field damage demonstrated a positive correlation. In glaucomatous eyes, as the amount of visual field damage increased, the FNR also increased. As expected, this relationship was not seen in the unaffected eyes that did not have visual field damage (Table 3). There was a significant difference among visual field loss categories in terms of the ΔFNR ($p < 0.001$). After Bonferroni adjustments ($p = 0.05/3 = 0.0167$), the difference between mild and moderate damage was not significant. Comparisons of mild versus severe damage ($p < 0.001$) and moderate versus severe damage ($p < 0.011$) were statistically significant. The relationship between FPR and the degree of visual field damage as measured by MD was not significant. For FLR, there was only a

Table 2. Mean false-negative rates (FNRs) associated with demographic factors.*

Variable	FNR, affected eyes (range)	FNR, unaffected eyes (range)	ΔFNR (range)	p Value
Overall	12.56 (0.00 - 100.00) [n = 290]	4.19 (0.00 - 50.00) [n = 295]	8.43 (-50.00 - 100.00) [n = 288]	<0.001†
Race				
Caucasian	11.21 (0.00 - 100.00) [n = 120]	4.24 (0.00 - 33.33) [n = 123]	7.26 (-18.00 - 100.00) [n = 120]	0.382‡
Black	13.90 (0.00 - 100.00) [n = 125]	4.15 (0.00 - 50.00) [n = 126]	9.66 (-50.00 - 33.33) [n = 123]	
Hispanic	12.65 (0.00 - 75.00) [n = 35]	4.37 (0.00 - 14.29) [n = 36]	8.15 (-14.29 - 75.00) [n = 35]	
Asian	11.77 (0.00 - 33.33) [n = 10]	3.33 (0.00 - 16.67) [n = 10]	8.34 (-16.67 - 33.33) [n = 10]	
Sex				
Male	13.73 (0.00 - 100.00) [n = 172]	3.98 (0.00 - 33.33) [n = 175]	9.96 (-20.00 - 100.00) [n = 172]	0.214§
Female	10.85 (0.00 - 54.54) [n = 118]	4.50 (0.00 - 50.00) [n = 120]	6.16 (-50.00 - 54.54) [n = 116]	
Socioeconomic status				
Upper (clinic A)	8.82 (0.00 - 66.67) [n = 74]	3.61 (0.00 - 50.00) [n = 74]	5.21 (0.00 - 66.67) [n = 74]	0.158‡
Middle (clinic B)	14.36 (0.00 - 100.00) [n = 88]	4.37 (0.00 - 33.33) [n = 90]	10.24 (-18.00 - 100.00) [n = 88]	
Lower (clinic C)	13.49 (0.00 - 75.00) [n = 128]	4.39 (0.00 - 50.00) [n = 131]	9.06 (-50.00 - 75.00) [n = 126]	

* Taken together, none of the demographic factors (race, sex, socioeconomic status) were statistically significant.
† p Value based on the Wilcoxon signed rank test.
‡ p Value based on the Kruskall-Wallis test.
§ p Value based on the Wilcoxon rank sum test.

Table 3. Mean false-negative rates (FNRs) associated with mild, moderate, and severe visual field loss.

Visual field loss*	FNR, affected eyes (range)	FNR, unaffected eyes (range)	ΔFNR (range)	p Value
Mild	6.69 (0.00 - 54.54) [n = 105]	3.68 (0.00 - 50.00) [n = 105]	3.01 (-50.00 - 54.54) [n = 105]	<0.001†
Moderate	11.56 (0.00 - 54.54) [n = 99]	4.48 (0.00 - 40.00) [n = 98]	7.08 (-27.50 - 54.54) [n = 98]	
Severe	20.88 (0.00 - 100.00) [n = 86]	4.47 (0.00 - 25.00) [n = 92]	16.69 (-14.28 - 100.00) [n = 85]	

* There was a borderline significant difference between mild and moderate degrees of field loss ($p = 0.059$). There was a statistically significant difference between mild and severe visual field loss ($p < 0.001$) and between moderate and severe visual field loss ($p = 0.011$).
† p Value based on the Kruskall-Wallis test.

Table 4. Mean deviation in affected eyes associated with demographic factors.

Variable	Mild (range)	Moderate (range)	Severe (range)	p Value
Overall	-4.96 (-11.53 to -0.34) [n = 104]	-7.85 (-23.34 to -1.85) [n = 94]	-19.43 (-30.97 to -4.88) [n = 83]	<0.001*
Race				
Caucasian	-4.58 (-11.53 to -0.57) [n = 43]	-7.27 (-21.68 to -1.85) [n = 35]	-18.77 (-30.15 to -9.77) [n = 34]	0.201†
Black	-5.39 (-10.48 to -0.74) [n = 46]	-7.91 (-23.34 to -3.00) [n = 42]	-19.93 (-30.97 to -4.88) [n = 34]	
Hispanic	-3.69 (-10.47 to -0.34) [n = 11]	-8.69 (-15.95 to -4.72) [n = 15]	-19.83 (-28.34 to -12.79) [n = 9]	
Asian	-7.65 (-11.20 to -3.36) [n = 4]	-10.51 (-16.72 to -10.50) [n = 2]	-19.65 (-23.28 to -15.09) [n = 3]	
Sex				
Male	-5.22 (-11.20 to -0.63) [n = 52]	-8.43 (-23.34 to -1.85) [n = 50]	-20.03 (-30.43 to -7.64) [n = 58]	0.833†
Female	-4.72 (-11.53 to -0.34) [n = 53]	-7.20 (-15.95 to -3.00) [n = 44]	-18.05 (-30.97 to -4.88) [n = 25]	
Socioeconomic status				
Upper (clinic A)	-3.91 (-9.89 to -0.34) [n = 35]	-7.11 (-23.34 to -1.85) [n = 22]	-15.25 (-30.43 to -4.88) [n = 14]	0.875†
Middle (clinic B)	-4.88 (-10.48 to -0.63) [n = 24]	-8.53 (-21.68 to -3.46) [n = 31]	-19.26 (-30.15 to -7.64) [n = 31]	
Lower (clinic C)	-5.82 (-11.53 to -0.74) [n = 45]	-7.89 (-16.72 to -3.00) [n = 50]	-21.12 (-30.97 to -5.85) [n = 38]	

* p Value based on the Kruskall-Wallis test.

† The difference in defects between the races, sexes, and socioeconomic levels were not statistically significant.

mild positive correlation with visual field damage, which was of borderline significance ($p = 0.054$).

Analysis of median MD in the glaucomatous eye is shown in Table 4. With respect to worsening visual field loss, the MD significantly decreased ($p < 0.001$). This trend held for all racial groups, sexes, and socioeconomic levels. Overall, MDs in patients with mild, moderate, and severe visual field loss were -4.76, -7.20, and -20.09, respectively.

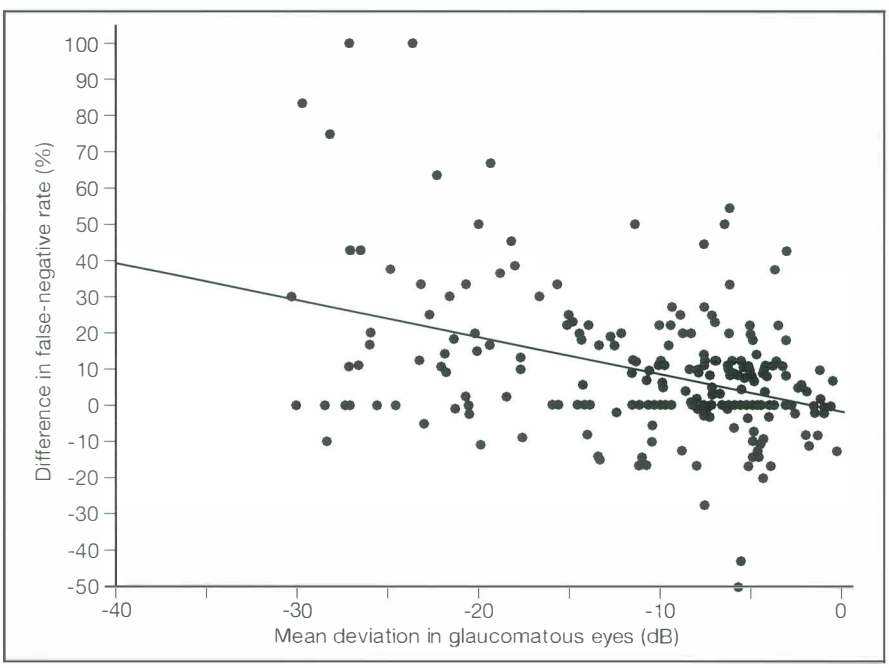
With respect to race, black patients had overall worse MDs than Caucasians for all categories of visual field loss. The difference among defects between the races was not significant. With respect to sex, men had worse MD scores than women at all levels of visual field loss. However, the difference among defects between the sexes was not significant. Patients from clinic A had the lowest mean MD values for all stages of visual field damage (-3.31, -6.31, and -13.75 for mild, moderate, and severe, respectively). The difference in defects between the clinics was not significant.

To investigate the combination of effects of socioeconomic status, race, sex, and age on in ΔFNRs, the following steps were carried out. First, each predictor was included individually in a model with MD and the interaction of the predictor and MD. There were no significant interactions. Next, the models were rerun, omitting the interaction terms. None of the predictors were significant in the presence of MD. Then, several pairwise interactions were included (sex-age, sex-clinic, race-clinic, etc) along with the corresponding main effects. None of these interactions were significant. Finally, all predictors were included in a model together (with no interaction terms), along with MD. None of the predictors were significant. These main effects were singly eliminated in order of least significance and the models were refit. At the end of this process, no predictors were significant in the presence of mean deviation.

Discussion

The relationship between MD and ΔFNR between eyes found by Bengtsson and Heijl[1] was corroborated in this study. This relationship is shown in the scatter plot with a linear regression line fit to the data (Figure 1). There was no relationship found with FPR or FLR. There was a borderline

Figure 1. Relationship between intrapatient intereye differences in false-negative rates (FNRs) and mean deviation (MD) in glaucomatous eyes. FNR_diff = -1.596709 - 1.014676*MD_affected.



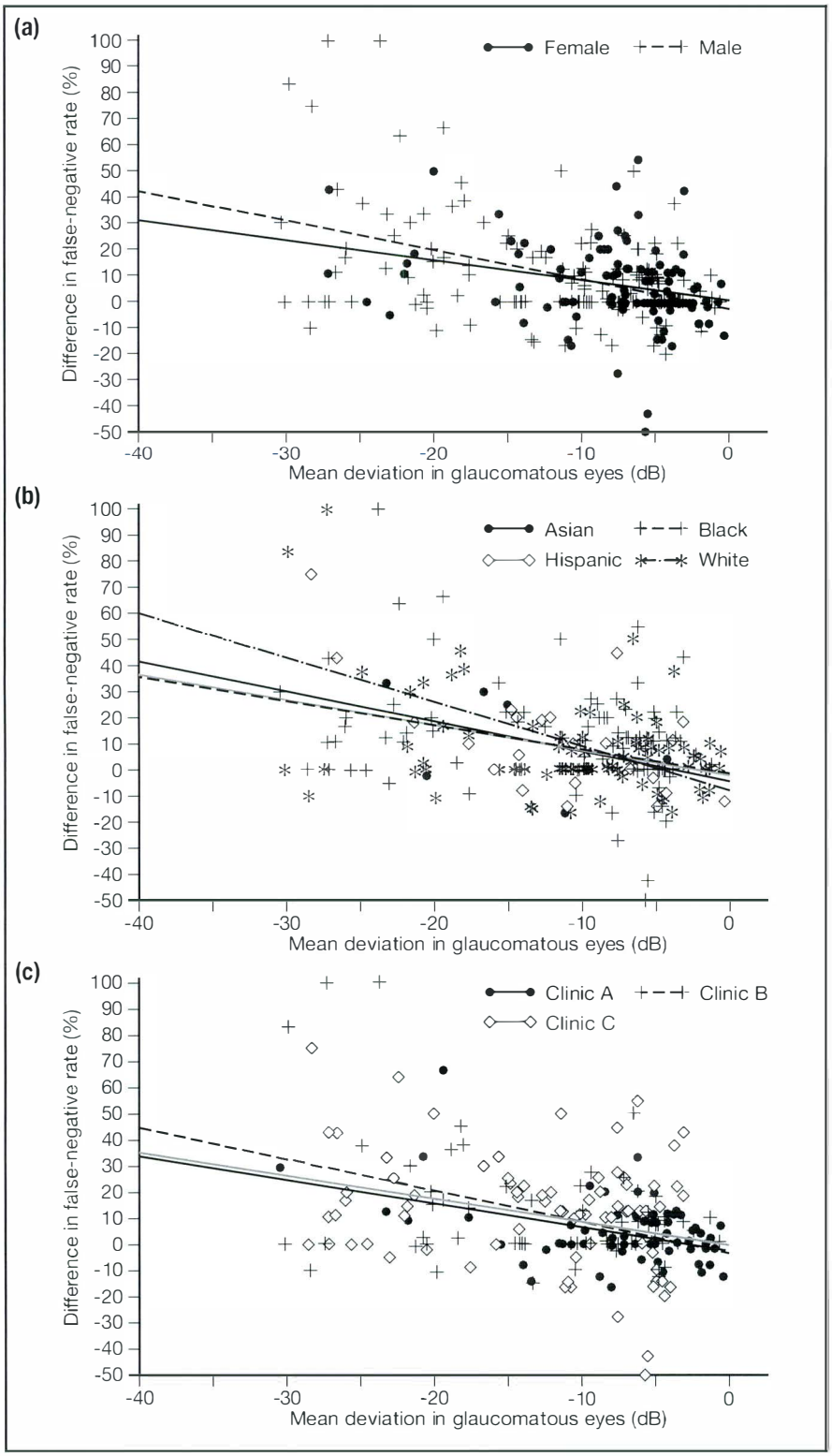
significant difference between mild and moderate degrees of visual field loss ($p = 0.059$). There was a significant difference between mild and severe damage ($p < 0.001$) and between moderate and severe damage ($p < 0.011$).

The role of sex, race, and socioeconomic status on ΔFNRs were evaluated with separate regression lines fit for each group (Figure 2). In this study, blacks tended to have higher FNRs than Hispanics, followed by Asians and, lastly, Caucasians, who had the lowest FNRs. Men tended to have higher FNRs than women. Patients from clinic C had a higher mean FNR than those from clinic B and patients of higher socioeconomic status (clinic A) had the lowest mean FNR. However, none of these demographic factors had a statistically significant effect on ΔFNR.

Although visual field analysis provides an acceptable means of evaluating glaucoma, the degree of the reliability depends on the patient's performance. Sensitivity and specificity rates for Humphrey glaucoma perimetry are lower for unreliable fields than for those considered reliable.[9] Both fixation losses and FNRs are more common among patients with glaucoma.[2] FLR is also the most common error for healthy and glaucomatous eyes and can reduce both sensitivity and specificity. Increased FPRs reduce sensitivity, while excess FNRs decrease specificity.

Originally, FNRs were thought to represent patient inattention or fatigue.[3-5] Katz and Sommer demonstrated that increased FNRs are more closely associated with glaucomatous eyes than with normal eyes or those with ocular hypertension.[2] Thus, FNRs may be more indicative of glaucomatous damage than of reliability.[3] Bengtsson and Heijl also showed that FNRs are associated with the amount of visual field damage.[1] However, their study focused primarily on the Swedish population. The role of race in glaucoma is well recognised.[10-13]

Figure 2. Relationship between intrapatient intereye differences of false-negative rates (FNRs) and mean deviation (MD) for sex, race, and socioeconomic status. (a) FNR_diff (Sex:Female) = 0.362563 - 0.763693*MD_affected, FNR_diff(Sex:Male) = -2.724057 - 1.110714*MD_affected; (b) FNR_diff(Race:Asian) = -4.846157 - 1.158106*MD_affected, FNR_diff(Race:Black) = 0.593972 - 0.87712*MD_ affected, FNR_diff(Race: Hispanic) = -7.988546 - 1.711148*MD_affected, FNR_diff(Race:Caucasian) = -1.91114 - 0.959512*MD_affected; and (c) FNR_diff(Clinic:A) = -1.751795 - 0.892577*MD_affected, FNR_diff(Clinic:B) = -0.051477 - 0.887671*MD_affected, FNR_diff(Clinic:C) = -3.134661 - 1.201259*MD_affected.



This study was unique in that it evaluated the cosmopolitan population of the Dallas metropolitan area, which comprises a variety of racial groups. In this study, the patient population was composed of 43% black, 41% Caucasian, 12% Hispanic, and 3% Asian.

The difference in FNRs among eyes with glaucoma and normal eyes has been shown to be independent of age, pupil diameter, and visual acuity.[14] In a study of a population with glaucoma from an urban area, most of whom came from an inner city area, fewer than two-thirds of Humphrey visual fields were reliable.[15] Influential factors included severity of visual field defect, length of test time, and age of the patient. This study sought to identify the role of demographic factors, particularly age, race, sex, and socioeconomic status, on FNR in a more cosmopolitan population from Dallas.

MD is considered a reliable index for monitoring visual fields.[16] In this study, blacks demonstrated worse MD scores (and more severe visual field loss) than Caucasians. Hispanics tended to have the least severe visual field loss in mild visual field damage, but had worse visual field loss than blacks and Caucasians for moderate visual field loss. In the late stages of the disease, blacks had worse visual field loss compared with all other races. Interestingly, although the subgroup was small, Asians did worse than all other races in the mild and moderate visual field loss categories. Men had worse MD scores than women for all stages of damage and were approximately 2 years older. According to CIGTS,[8] qualitative factors towards variability in this score include factors such as male sex, black race, decreased alertness, lower visual acuity, higher IOP (>30 mm Hg), poor field reliability, cardiovascular disease, and testing centre. The data from this study demonstrate several interesting patterns in MD, although it did not evaluate these other possible confounding factors.

In terms of socioeconomic status, individuals in the higher socioeconomic group had the least amount of damage during all stages of the disease process. Those from clinic B had worse damage in the mild and moderate stages of disease. These patients also tended to be approximately 7 years older than patients from the other clinics and also had more concomitant medical problems such as diabetes and hypertension. On the basis of MD, individuals in the lower socioeconomic group (clinic C) had the most severe visual field loss in the early stage as well as at the end of the disease process, with the highest MD. These data may be a result of earlier detection and screening in individuals of higher socioeconomic status and poorer compliance in those of lower socioeconomic status. As assignment of socioeconomic status was done by hospital site (which may not accurately represent true socioeconomic status) instead of income, there was a bias towards the null hypothesis in this cross-sectional study.

Frequently, it is difficult to distinguish visual fields of healthy eyes from those with early glaucoma. Some clinicians consider that in early glaucoma, localised scatter on automated perimetry testing may be a reliable precursor.[17] The Glaucoma Hemifield Test algorithm takes advantage of the asymmetry of glaucomatous field loss across the horizontal meridian; this algorithm is useful for detecting early visual field loss, yielding a sensitivity of 100% and a specificity of 84%.[18,19] Experience with automated perimetry and the learning effect may play a role,[20] although several studies refute this theory.[21] This aspect was not assessed in this study because patients without prior experience of visual field testing were excluded from the study.

There were several limitations of this study. This was a retrospective chart review, with associated selection bias. As stated earlier, there was also a bias towards the null hypothesis because the patients were assigned to certain socioeconomic groups on the basis of their hospital site, whereas socioeconomic status should be based on income. The sample size, although larger than in prior studies, was not large. To detect a significant difference between the 4 races, 1147 people in each racial group would be needed; this study had 12% power. To detect a statistically significant difference between the sexes, 337 men and 337 women would be required; this study had 46% power. To detect a significant difference between the clinics, 213 patients would be needed in each of the 3 groups to achieve 80% power; this study had 45% power.

The study could not demonstrate that FNR-related visual field loss was affected by age, race, sex, or socioeconomic status. In this highly selected retrospective cross-sectional study, blacks, men, and individuals of lower socioeconomic status were most severely affected by glaucomatous visual field loss.

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References

1. Bengtsson B, Heijl A. False-negative responses in glaucoma perimetry: indicators of patient performance or test reliability? Invest Ophthalmol Vis Sci 2000; 41:2201-2203.
2. Katz J, Sommer A. Screening for glaucomatous visual field loss: the effect of patient reliability. Ophthalmol 1990;97: 1032-1037.
3. Katz J, Sommer A, Witt K. Reliability of visual field results over repeated testing. Ophthalmol 1988;95:764-767.
4. Lachenmayr BJ, Vivell PMO. Perimetrie. Stuttgart: Thieme; 1992:37.
5. Choplin NT, Russell PE. Visual field testing

with the Humphrey analyzer. Thorofare: Slack; 1995.
6. Budenz DL. Atlas of visual fields. Philadelphia: Lippincott-Raven; 1997.
7. The AGIS Investigators. The advanced glaucoma intervention study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. Am J Ophthalmol 2002;134:499-512.
8. Gillsepie BW, Musch DC, Guire KE, et al; CIGTS (Collaborative Initial Glaucoma Treatment Study) Study Group. The collaborative initial glaucoma treatment study: baseline visual field and test-retest variability. Invest Ophthalmol Vis Sci 2003; 44 2613-2620.
9. Enger C, Sommer A. Recognizing glaucomatous field loss with the Humphrey STATPAC. Arch Ophthalmol 1987;105: 1355-1357.
10. Wilson R, Richardson, TM, Hertzmark E, Grant WM. Race as a risk factor for progressive glaucomatous damage. Ann Ophthalmol 1985;17:653-659.
11. Wilson MR, Hertzmark E, Walker, AM, Childs-Shaw K, Epstein DL. A case-control study of risk factors in open angle glaucoma. Arch Ophthalmol 1987;106:1066-1671.
12. Leske MC, Connell AMS, Schachat AP, Hyman L. The Barbados eye study. Arch Ophthalmol 1994;112:821-829.
13. Martin MJ, Sommer A, Gold EB, Diamond EL. Race and primary open-angle glaucoma. Am J Ophthalmol 1985;99:383-387.
14. Birt CM, Shin DH, Samudrala V, Hughes BA, Kim C, Lee D. Analysis of reliability indices from Humphrey visual field tests in an urban glaucoma population. Ophthalmology 1997;104:1126-1130.
15. Katz J, Sommer A. Reliability indexes of automated perimetric tests. Arch Ophthalmol 1988;106:1252-1254.
16. Flammer J, Drance SM, Augustiny L, Funkhouser A. Quantification of glaucomatous visual field defects with automated perimetry. Invest Ophthalmol Vis Sci 1985; 26:176-181.
17. Werner EB, Drance SM. Increased scatter as a precursor of visual field changes in glaucoma. Can J Ophthalmol 1997;1:140.
18. Asman P, Heijl A. Glaucoma hemifield test: automated visual field evaluation. Arch Ophthalmol 1992;110:812-819.
19. Sommer A, Enger C, Witt K. Screening for glaucomatous visual field loss with automated threshold perimetry. Am J Ophthalmol 1987;103:681-684.
20. Heijl A, Lindgren G, Olsson J. The effect of perimetric experience in normal subjects. Arch Ophthalmol 1989;107:81-86.
21. Werner EB, Adelson A, Krupin T. Effect of patient experience on the results of automated perimetry in clinically stable glaucoma patients. Ophthalmol 1988;94: 764-767.

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Clinical Study of Ophthalmopathy in Patients with Graves' Disease

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Aim: *The aim of this study was to evaluate ophthalmopathy in patients with Graves' disease according to sex, age, and duration of the disease.*
Patients and Methods: *Ninety five patients with Graves' disease were included in the study. Sixty two percent of patients were women and 38% were men. All patients underwent a complete ophthalmic examination.*
Results: *The frequency of ophthalmopathy was 60%. The most common signs were proptosis and eyelid retraction. Intraocular pressure and occurrence of chemosis were significantly higher among men than among women. Eye lesions occurred more frequently in patients aged between 50 and 70 years. In addition, the frequency of chemosis, periorbital oedema, corneal irritation, convergence insufficiency, diplopia, and proptosis had a positive correlation with age. Only 16% of patients had ophthalmic complaints alone during the first visit. The incidence of lid retraction decreased during the course of the disease, but the severity of chemosis, conjunctival congestion, and extraocular muscle enlargement increased with longer duration of the disease.*
Conclusion: *The findings of this study are similar to those of previous studies, although there are some differences, notably a higher incidence of proptosis and lid retraction.*

Key words: *Graves' disease, Hyperthyroidism*

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Introduction

Graves' disease was first recognised by the Iranian scientist Sayyid Ismail Al-Jurjani,[1,2] who described the relationship between exophthalmos and the disease in the twelfth century.[2] Later, Parry et al further described the condition and it was recognised as Graves' disease in 1835.[2] Graves' disease usually occurs in conjunction with hyperthyroidism, although patients may be euthyroid. Ophthalmopathy is most commonly observed among patients who have active or treated Graves' disease. However, ophthalmopathy is also observed in patients who have Hashimoto's disease, primary hyperthyroidism, carcinoma of the thyroid, or other forms of thyroid disease such as thyroiditis.[2,3] The male to female ratio of patients with systemic hyperthyroidism is 4:1, whereas the male to female ratio for patients with ophthalmopathy is 2.5:1.[4] More than half of the patients who have hyperthyroidism present with ophthalmological signs and symptoms at some time during the course of the disease, and these signs and symptoms could be unilateral or bilateral, or mild to severe. These ophthalmological signs can appear before other signs of hyperthyroidism or even after regression of the disease.[4] Therefore, ophthalmological signs may lead to a diagnosis of Graves' disease. This study was conducted to investigate ophthalmological signs and symptoms of Graves' disease in Iran.

Patients and Methods

This study used a descriptive cross-sectional design. The study population consisted of 95 consecutive patients with Graves' disease who were referred to the endocrinology clinic at Afshar Hospital, the ophthalmological clinic at Shahid Rahnemoon Hospital, and private clinics in Yazd, Iran, between January 2001 and June 2002.

Hyperthyroidism was diagnosed using serological tests, including those for tri-iodothyronine, thyroxine, thyrotropin, T_3 resin uptake, free thyroxine, free tri-iodothyronine, and antiperoxidase antibody. The patients underwent an ophthalmological examination, which included visual acuity, examination by Haag Streit slit lamp, measurement of intraocular pressure (IOP) by applanation tonometry, exophthalmometry using the Hertel exophthalmometer, examination of eyelid and globe position, and external ocular muscle movement using the cover test, corneal light reflex and forced duction test, fundoscopy to check the status of the optic nerve, and computed tomography (CT) or magnetic resonance imaging (MRI) when required. All clinical findings and personal details were noted in a specially designed questionnaire.

The dependent variables were ophthalmic signs and symptoms; independent variables included age, sex, duration of illness, and treatment. Data were analysed using the Statistical Package for the Social Sciences (Chi squared and Fisher exact tests, and analysis of variance).

Results

Of the 95 patients with Graves' disease evaluated in this study, 62.1% were women and 37.9% were men. The mean age of the patients was 36.5 years (range, 16 to 70 years), with 31.6% of patients in the 16- to 29-year age group, 53.7% in the 30- to 49-year age group, and 14.7% in the 50- to 70-year age group.

Table 1. Prevalence of ophthalmopathy by age.

Age group (years)	Number of patients	Ophthalmopathy		
		Unilateral Number (%)	Bilateral Number (%)	Total Number (%)
16-29	30	10 (33.3)	7 (23.3)	17 (56.7)
30-49	51	8 (15.7)	24 (47.1)	32 (62.7)
50-70	14	—	8 (57.1)	8 (57.1)
Total	95	18 (18.9)	39 (41.1)	57 (60.0)

Ophthalmopathy was present in 60.0% of the study population (95% confidence interval, 50.2%-69.8%). Ophthalmopathy was present in 23 of 36 men (63.9%) and 34 of 59 women (57.6%). This difference was not statistically significant. The incidence of ophthalmopathy was similar in all age groups, but the incidence of bilateral ophthalmopathy was significantly higher than unilateral ophthalmopathy with increasing age ($p = 0.006$). In general, the occurrence of bilateral ophthalmopathy was greater than that of unilateral disease, with a ratio of 2.2:1; the ratio was 3:1 in the 30- to 49-year age group. No cases of unilateral ophthalmopathy were detected among the patients aged 50 years or older (Table 1).

The most common ocular signs among the study population were exophthalmos or proptosis (49.5%) and eyelid retraction (48.4%). Proptosis was detected in 47 patients, of which 14 cases were unilateral and 33 were bilateral. The majority of these patients (30 of 47; 63.8%) were aged 30 to 49 years. None of the patients had optic neuritis or papillitis (Figure 1).

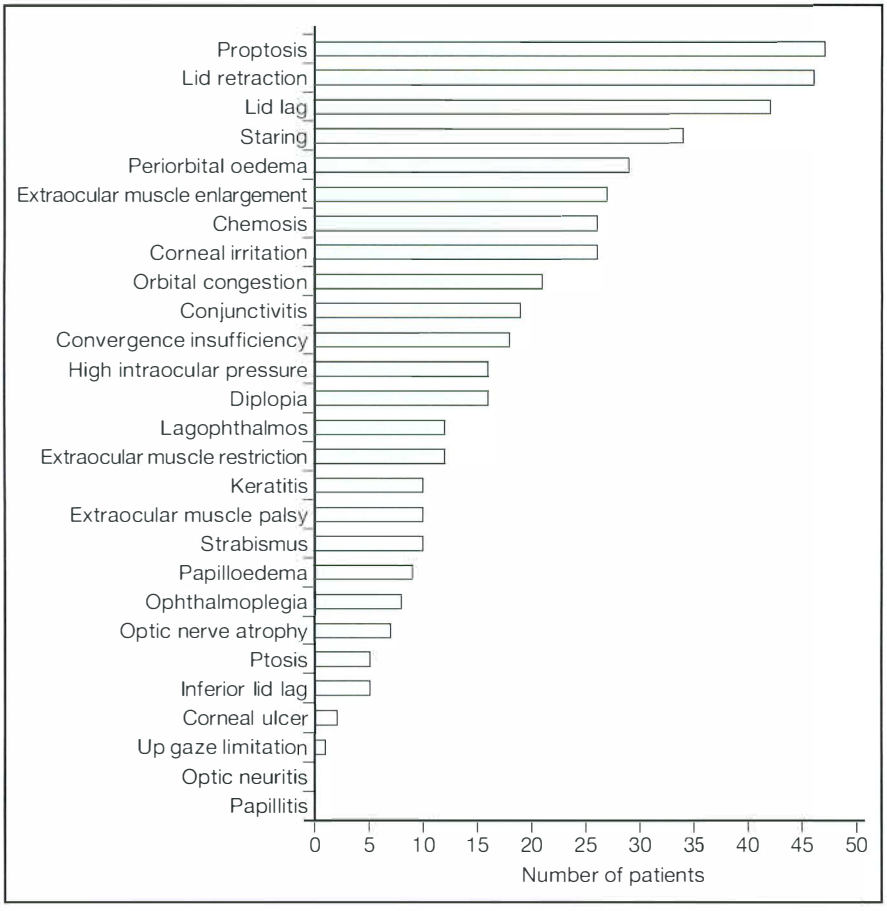
The frequencies of ocular complications were different for each age group. The prevalence of lid lag, diplopia, increased blinking, ptosis, proptosis, staring, strabismus, chemosis, periorbital oedema, and corneal irritation increased with age, whereas the frequency of lid retraction decreased with age. The frequencies of ophthalmological signs in the different age groups were as follows:

- 16 to 29 years — lid retraction (53.3%), proptosis (30.0%), and lid lag (30.0%)
- 30 to 49 years — proptosis (56.9%), lid retraction (51.0%), and lid lag (47.1%)
- 50 to 70 years — proptosis (64.2%), periorbital oedema (57.1%), and lid lag, enlargement of extraocular muscle (EOM) on CT scan, and chemosis (50.0%).

The mean numbers of ocular findings in the different age groups were as follows: 1.9 in the 10- to 29-year age group, 6.1 in the 30- to 49-year age group, and 6.9 in the 50- to 70-year age group, suggesting that the number of ocular findings increases with age. In addition, the number of ocular findings was greater for men than for women (9.6 versus 7.2, respectively).

The prevalence of ocular findings by sex were as follows: proptosis — men, 61.1%; women, 42.4%; lid retraction — men, 50.0%; women, 47.5%; and lid lag — men, 42.2%; women, 42.4%. Increase in IOP and chemosis were noted more frequently in men than in women ($p = 0.007$ and $p = 0.049$, respectively). The differences between men and women for the other ocular findings were not statistically significant. The prevalence of lid retraction, lid lag, ptosis, periorbital oedema, limitation of ocular motility, orbital congestion, convergence insufficiency, EOM enlargement on CT scan, keratitis, proptosis, ophthalmoplegia, and optic atrophy were more common among men, whereas increased blinking and strabismus were more common among women.

Figure 1. Frequency of ocular signs and symptoms.



The frequency of lid retraction decreased with increased duration of disease ($p = 0.029$). In contrast, EOM enlargement on CT scan ($p = 0.047$), chemosis ($p = 0.009$), and eye congestion ($p = 0.22$) increased with increased duration of disease.

Thyroid ophthalmopathy was noted in 43.8% of patients 18 months from the diagnosis of Graves' hyperthyroidism, in 24.6% of patients between 18 months and 5 years, and in 31.4% after 5 years. The most common complaints at the first consultation were non-ocular signs (50.5%), followed by concomitant ocular and non-ocular signs (28.4%), and ocular signs alone (15.8%). The initial complaint was unknown for 5.3% of patients. Orbital CT was performed for 38 of the 57 patients with ophthalmopathy. EOM enlargement was noted in 27 patients (71.1%).

Discussion

In thyroid eye disease (TED), the eyes are usually involved asymmetrically and rarely involved unilaterally. Therefore, for unilateral proptosis, assessment for retrobulbar tumour is necessary.[4] In this investigation, bilateral ophthalmopathy occurred more frequently than unilateral ophthalmopathy and the frequency increased with age — all the patients with ophthalmopathy in the 50- to 70-year age group had bilateral ophthalmopathy. In general, ophthalmopathy was seen more frequently in women than in men (1.5:1). A total of 60.0% of patients had ophthalmopathy, with the greatest overall prevalence (unilateral or bilateral) observed in the 30- to 49-year age group. The most common signs of ophthalmopathy were proptosis (49.5%) and lid retraction (48.4%). None of the patients had optic neuritis.

In the study by Sieradzki et al, risk factors for ophthalmopathy included recurrent hyperthyroidism, late diagnosis, delay in treatment, and no treatment with thyroxine.[5] Hypertrophy of EOM alone is not considered to be active disease or a risk factor for TED.[6]

Graves' ophthalmopathy is associated with extensive ocular morbidity in more than 90% of patients with hyperthyroidism. One of the most valuable diagnostic tests for ophthalmopathy is an orbital CT scan, in conjunction with a clinical examination and thyroid function tests.[7] In this study of 57 patients with ophthalmopathy, 38 underwent CT. The CT scan showed hypertrophy of the EOM in 27 patients (71.1%).

In a long-term follow-up study (mean, 9.8 years) of 120 patients, Bartley et al found a 2.2% visual acuity decrease secondary to optic neuropathy and constant diplopia.[8] Of one-third of patients with eye discomfort, the most common complaint was dry eye (72%). In total, 60.5% of the patients believed that the size of their eyes had not returned to normal and 40.0% were not satisfied with the apparent condition of their eyes. Park et al showed that thyroid ophthalmopathy affects quality of life,[9] although this was not evaluated in the study presented here.

Bartley also showed that the ratio of women to men was 1:0.6 with a bimodal incidence in the 40- to 44-year and 60- to 64-year age groups.[10] Approximately 90% of the patients had hyperthyroidism, 3% had Hashimoto's disease and 5% had euthyroidism. Unilateral or bilateral lid retraction was the most common sign in 90% of patients. Unilateral or bilateral lid lag was common and was noted in 50% of patients during the primary clinical examination. At the time of diagnosis of Graves' disease, the most common ophthalmological symptom was pain (30%). Signs and symptoms that significantly changed between the first and the final visits included tearing, pain, ocular discomfort, photophobia, lid retraction, lid lag, conjunctival injection, chemosis, lid fullness, and exophthalmia.

In a clinical review by Carter, ophthalmopathy was present in 2% to 7% of patients with Graves' hyperthyroidism and the main manifestations were proptosis, ophthalmoplegia, optic neuropathy, and lid retraction.[11] In this study, the most common manifestations among men were proptosis (61.1%), lid retraction (50.0%), and lid lag (42.2%); among women, they were lid retraction (47.5%), lid lag (42.4%), and proptosis (42.4%).

Marcocci et al showed that there is no clear relationship between treatment of hyperthyroidism and the course of ophthalmopathy. Antithyroid drugs may improve ocular manifestations, whereas prescription of radioactive iodine and thyroidectomy cause worsening of ophthalmopathy.[12] Emergency conditions associated with Graves' ophthalmopathy include optic neuropathy, corneal ulceration, globe subluxation, and periorbital oedema with chemosis. Early diagnosis and treatment is important, as there is a direct relationship between decreased vision and the effect of treatment.[13]

Ampudia et al investigated the occurrence of exophthalmos diagnosed by Hertel exophthalmometry and CT.[14] Exophthalmos by Hertel exophthalmometry was measured as 22.5 ± 2.5 mm for the right eye and 23.2 ± 3.2 mm for the left eye. The measurements made by CT were smaller (20.8 ± 3.2 mm and 20.9 ± 2.9 mm for the right and left eyes, respectively) but this difference was not statistically significant. The study showed that the muscles were not equally involved and the medial rectus and inferior rectus muscles were most commonly involved. The width of the medial rectus muscle was not related to the course or severity of the disease.

Treatment of Graves' disease with radioactive iodine causes exacerbation of ocular signs that can be prevented by administration of prednisolone.[15] Orbital decompression using the nasal approach results in visual improvement and reduction of proptosis.[16]

Thyroid-associated ophthalmopathy (TAO) may appear before, during, or after systemic presentations of thyroid disease. For 20% of patients, ocular complaints such as lid retraction, proptosis, chemosis, periorbital oedema, ocular motility changes, and cosmetic problems are of greater concern than thyroid disease.[17] Strabismus is common in TAO and usually presents in hypotropic or esotropic form. In this study, 21% of patients had strabismus, the majority of whom had hypotropia or esotropia. Strabismus was more common in women than in men (1.5:1). Anterior segment symptoms included corneal irritation secondary to dry eye (27.0%), keratitis (10.5%), conjunctivitis (20.0%), chemosis (27.0%), high IOP (17.0%), and upper eyelid ptosis (5.2%). Visual field and colour vision tests may help to detect early decreased visual function.[17]

Inferior rectus restriction can mimic double elevator palsies. Regulation of thyroid function does not improve TAO and may worsen the condition in some euthyroid patients. In patients with hyperthyroidism, ophthalmopathy usually occurs within 18 months of disease onset. This study also showed this result. If TAO is clinically diagnosed, there is no need for further imaging, but if imaging is necessary, MRI is more sensitive than CT to show compression of the optic nerve,[14,18] although CT is required for optic nerve decompression to visualise the orbital bony structures.[19]

Thyroid ophthalmopathy is clinically apparent in approximately 50% of patients with Graves' disease.[2] In this study, the rate was 60.0%, which is similar to that reported by Vangheluwe et al[19] (62.3%), but lower than the rates reported by Nordyke et al[20] (91.4%) and Bartley et al[8] (90.0%).

The ratio of women to men with ophthalmopathy was 2.5:1 in the study by Devron and Char,[21] 2.7:1 in that by Wiersinga et al,[22] and 6:1 in that by Vangheluwe et al.[19] In this study, the ratio of women to men with ophthalmopathy was lower at 1.5:1.

Ophthalmopathy was more prevalent in the 30- to 49-year age group, which is similar to the study by Nordyke et al,[20] with the most commonly affected age group being 30 to 50 years, and that by Teshome and Seyoum[23] with a mean affected age of 35 years. Other studies have shown ophthalmopathy occurring more frequently in the higher age groups. The mean age of affected patients in the study by Wiersinga et al[22] was 44.5 years while, in the study by Marcocci and Bartalena,[24] ophthalmopathy was more prevalent in the fifth decade. In the study by Vangheluwe et al, ophthalmopathy was more prevalent in the 40- to 44-year and 60- to 64-year age groups in women and in the 45- to 49-year and 65- to 69-year age groups in men.[19] The mean age was 43 years, which was the same as in the study by Bartley et al.[8]

Unilateral involvement was reported to be 10% to 20% by Gorman[25] and 14% by Wiersinga et al.[22] The rate of unilateral involvement of 31.6% in this study was higher than in the studies by Gorman[25] and Wiersinga et al[22] but the rate was lower than that reported by Devron and Char[21] (66.0%). Ocular involvement during the first examination was detected in 15.8% of patients in this study. This rate was 5.0% to 25.0% in the study by Gorman[25] and 3.7% in the study by Bartley et al.[8]

The most common ocular signs among patients with thyroid ophthalmopathy in this study were proptosis (47; 82.4%) and lid retraction (46; 80.7%). The rate of proptosis in this study was higher than that found by Wiersinga et al[22] (30%), Bartley et al[8] (62.0%), and Vangheluwe et al[19] (60.0%). The rate of lid retraction in this study was similar to or slightly lower than the rates reported by Eden and Trotter[3] (94.0%), Bartley et al[8] (90.0%), Vangheluwe et al[19] (90.0%), and Teshome and Seyoum[23] (83.8%). Furthermore, the prevalence of lid lag in this study was 73.6% (42 patients), which was higher than the rates reported by Vangheluwe et al[19] (50.0%) and Gruters[26] (37.0%).

The prevalence of restrictive myopathy in the studies by Vangheluwe et al[19] and Bartley et al[8] were 40% and 43%, respectively. In this study, the prevalence of EOM involvement and convergence insufficiency was 35%.

The incidence of diplopia in this study was 28.1%, which was higher than that reported by Vangheluwe et al[19] (17.0%) and Bartley et al[8] (16.6%). The rates of exophthalmia and corneal damage reported by Wiersinga et al[22] were 30.0% and 9.0%, respectively, and by Vangheluwe et al[19] were 26.4% and 7.5%, respectively. In this study, the rates were 82.4% and 3.5%, respectively. The rate of ocular and orbital inflammation in this study was 57.8%, which is similar to 50.9% reported by Vangheluwe et al.[19] In this study, the rate of euthyroid ophthalmopathy was 5.2%, which is similar to the rate of 5.0% reported by Vangheluwe et al.[19] The rate reported by Marcocci and Bartalena[24] was 8.6% and by Teshome and Seyoum[23] was 13.5%.

The incidences of different signs and symptoms of ophthalmopathy in Graves' disease have been the subject of many studies. This study was conducted to evaluate these incidences in Iran. The data showed that many of the findings were similar to those of other investigation, although there were also some differences. Proptosis and lid retraction were the most important signs of the disease and proptosis mostly occurred in the 30- to 49-year age group. The prevalence of proptosis in this study was higher than in other studies. The prevalence of most of the ocular complications increased with increasing age, but the frequency of lid retraction decreased with age. The incidence of bilateral ophthalmopathy was significantly higher than that of unilateral ophthalmopathy among older patients. IOP and chemosis had a significantly higher frequency among men

than women. The most common complaints at the time of referral were non-ocular, although most cases of ophthalmopathy occurred during the first 18 months after diagnosis of Graves' hyperthyroidism. Graves' ophthalmopathy was found to be more common among women. As many affected patients were middle-aged women, the importance of functional and cosmetic consequences should be considered in the context of early diagnosis and treatment.

References

1. Rolleston HD. The endocrine organs in health and disease with an historical review. London: Oxford University Press; 1936.
2. Netland PA. Dallow KL. Thyroid ophthalmopathy. In: Albert DM, Jakobiec FA, editors. Principles and practice of ophthalmology. Vol 5. Philadelphia: WB Saunders Company; 1994:2937-2951.
3. Misconceptions in thyroid eye disease. 2003. http://gateway.proquest.com
4. Javadian A, Bahrami A, Izedyar S. Ophthalmic signs and symptoms of systemic diseases. Tehran: Hyan Cultural Organization Publications; 1998:20-21.
5. Sieradzki J, Katra B, Mirkiewic-Sieradzka B. Risk factors for occurrence of ophthalmopathy in the course of Graves-Basedow disease. Prezegl Lek 2000;57:321-323.
6. Nagy EV, Toth J, Kaldi I, et al. Graves' ophthalmopathy: eye muscle involvement in patients with diplopia. Eur J Endocrinol 2000;142:591-597.
7. Gracia Naya M, Uson M, Lopez-Lopez A, Tapiador MJ, Ara JR. Thyroid ophthalmopathy as a unique clinical manifestation of thyrotoxicosis. Rev Neurol 1995;23: 1059-1062.
8. Bartley GB, Fatourechi V, Kadrmas EF, et al. Long-term follow-up of Graves' ophthalmopathy in an incidence cohort. Ophthalmology 1996;103:958-962.
9. Park JJ, Sullivan TJ, Mortimer RH, Wagenaar M, Perry-Keene DA. Assessing quality of life in Australian patients with Graves' ophthalmopathy. Br J Ophthalmol 2004;88:75-78.
10. Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. Trans Am Ophthalmol Soc 1994;92: 477-588.
11. Carter JN. Graves' ophthalmopathy — a clinical review. Aust NZ J Ophthalmol 1990; 18:239-342.
12. Marcocci C, Bartalena I, Bogazzi F, Bruno-Bossio G, Pinchera A. Relationship between Graves's ophthalmopathy and type of treatment of Graves' hyperthyroidism. Thyroid 1992;2:171-178.
13. Bahn RS, Bartley GB, Gorman CA. Emergency treatment of Graves' ophthalmopathy. Baillieres Clin Endocnnol Metab 1992;6:95-105.
14. Ampudia J, Guardia E, Castrillo P, Cutillas M, Soldevila J, De-Leiva A. Thyroid ophthalmopathy: clinical and tomographic study. Med Clin (Barc) 1993;100:447-449.
15. Bartalena L. Hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998;338:73-78.
16. Michel O, Oberlander N, Neugebauer P, Neugebauer A, Russmann W. Follow-up of transnasal orbital decompression in severe Graves' ophthalmopathy. Ophthalmology 2001;108:400-404.
17. Edseling MD. Thyroid ophthalmopathy. E-med 2002; March.
18. Selva D, Chen C, King G. Late reactivation of thyroid orbitopathy. Clin Exper Ophthalmol 2004;32:46-50.
19. Vangheluwe O, Ducasse A, Vaudrey C, Maes B, Delisle MJ, Segal A. Prevalence of eye diseases in Basedow diseases. Apropos of a prospective study with 85 cases. J Fr Opthalmol. 1992;15: 469-473.
20. Nordyke RA, Gilbert FI, Harada A. Graves' disease, influence of age on clinical findings. Arch Intern Med 1988;148: 626-631.
21. Devron H, Char A. Thyroid eye disease. 2nd ed. London: Churchill Livingstone Inc; 1990:35-63.
22. Wiersinga WM, Smit T, van der Gaag R, Mourits M, Koornneef L. Clinical presentation of Graves' ophthalmopathy. Ophthalmic Res 1989;21:73-82.
23. Teshome T, Seyoum B. Graves' thyroid ophthalmopathy in Ethiopian patients. Ethiop Med J 2001;39:1-8.
24. Marcocci C, Bartalena L. Studies on the occurrence of ophthalmopathy in Graves' disease. Acta Endocrinol 1989;120: 473-478.
25. Gorman CA. Temporal relationship between onset of Graves' ophthalmopathy and diagnosis of thyrotoxicosis. Mayo Clin Proc 1983;58:515-519.
26. Gruters A. Ocular manifestations in children and adolescents with thyrotoxicosis. Exp Clin Endocrinol Diabetes 1999;107 (Suppl 5):172-174.

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Nasopharyngeal Carcinoma Presenting as Exudative Retinal Detachment, Haemorrhagic Choroidal Detachment, and Secondary Angle Closure Glaucoma

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This report is of a 68-year-old woman with an unusual association of anaplastic nasopharyngeal tumour and exudative retinal detachment, subsequent choroidal haemorrhage, and high intraocular pressure. The patient had unexplained poor vision after cataract surgery and developed a bullous exudative retinal and choroidal detachment and angle closure glaucoma 5 years later. Computed tomography revealed a tumour involving the contralateral right nasal cavity without direct extension into the left orbit. Histopathological examination of the tumour showed an undifferentiated nasopharyngeal carcinoma. Retrospective review of the left fundus fluorescein angiogram taken 5 years earlier suggested pigmentary changes and peripheral exudation. Similar pigmentary changes were evident in the fellow eye in association with subtle serous detachments and poor vision.

Key Words: Glaucoma, angle-closure, Nasopharyngeal neoplasms, Retinal detachment

Asian J Ophthalmol 2005;7(3):113-115.

Introduction

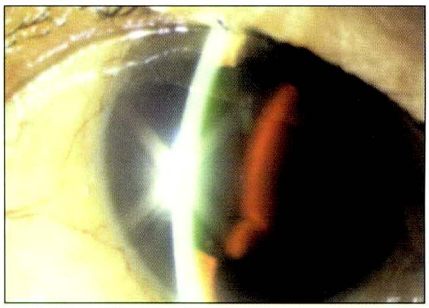
Exudative retinal detachment (ERD) is usually caused by intraocular inflammation but may, rarely, be associated with malignancy. Tumours commonly associated with ERD include uveal melanoma,[1] lymphoma,[2] and metastatic disease.[3] Occult malignancies may also cause ocular manifestations of a paraneoplastic syndrome such as carcinoma-associated retinopathy (CAR) or diffuse uveal melanocytic proliferation (DUMP).[4] Nasopharyngeal carcinoma (NPC) has not previously been reported to be associated with ERD, CAR, or DUMP.

Case Report

A 68-year-old Malay woman who had unexplained poor vision (6/36) in her left eye after uncomplicated left extracapsular cataract surgery 5 years previously presented in 2004 with sudden painful deterioration of vision with exudative retinal and choroidal detachment. Her vision deteriorated to perception of light as the eye developed a total haemorrhagic choroidal detachment and secondary angle closure 2 days after presentation (Figure 1). Her intraocular pressure was 45 mm Hg but was controlled with maximum medical therapy. Gonioscopy showed a 360° closed angle. Her right eye had perception of light vision owing to a dense right cataract; vision improved to counting fingers after uncomplicated phacoemulsification surgery performed in 2004.

Her relevant medical history included treatment with warfarin following insertion of a prosthetic heart valve for chronic rheumatic heart disease and haemoglobin H disease (α-thalassaemia) with chronic anaemia (international normalised ratio, 3.41 [therapeutic range for oral anticoagulation, 2.1-4.8]; haemoglobin, 68 g/L [normal range, 120-150 g/L]; and platelets, 158 x 10^9/L [normal range, 150-450 x 10^9/L]).

Figure 1. Anterior segment photograph of the left eye showing haemorrhagic detachment visible through a dilated pupil. This photograph was taken 2 days after presentation.



Computed tomography of the head revealed an enhancing lobulated mass in the right nasopharynx that measured 2.6 x 2.0 cm; there was no globe or orbital infiltration (Figure 2). Biopsy and histopathological examination of the lesion confirmed an undifferentiated NPC. Radiotherapy was initiated but the patient died suddenly from myocardial infarction 2 weeks later, before ocular electrophysiological tests could be performed. Autopsy was not performed.

Figure 2. Computed tomography image showing axial section of the brain at the level of the orbit and nasopharynx revealing a mass in the right nasopharynx contralateral to the exudative detachment in the left eye.

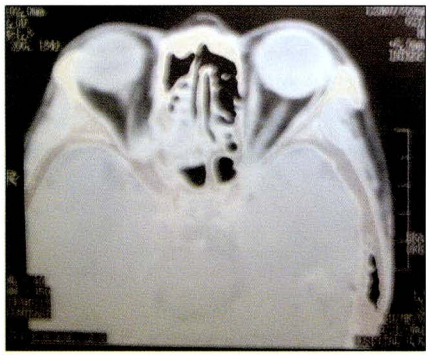
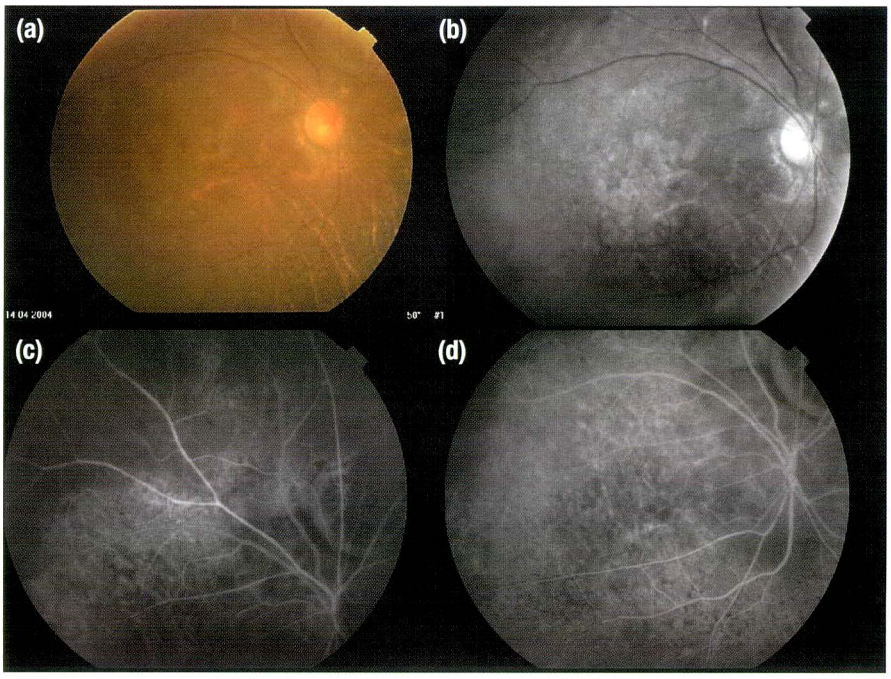


Figure 3. Findings in the patient's right eye following uncomplicated cataract extraction. (a) Colour fundus photograph showing widespread pigmentary changes; (b) red-free photograph highlighting the contrast between pigmented and less pigmented areas; (c) fundus fluorescein angiogram showing the right superior temporal retina with peripheral exudation; and (d) fundus fluorescein angiogram of the right posterior pole demonstrating choroidal hyperfluorescence in relation to the pigmentary changes. Similar findings were noted in the patient's left eye 5 years previously.



Retrospective review of a left fundus fluorescein angiogram that had been obtained 5 years previously showed widespread pigmentary changes and subtle areas of peripheral exudation. Fundus fluorescein angiography performed after the uncomplicated cataract surgery of her right eye showed similar pigmentary changes, peripheral exudation, subtle serous detachments, and poor vision (Figure 3).

Discussion

The ocular presentation of NPC is usually associated with sixth cranial nerve palsy and other features of direct invasion. This patient is therefore unusual, with intraocular presentation of NPC as part of a paraneoplastic syndrome. There are a number of possibilities for the patient's initial poor vision following cataract surgery. One hypothesis for unexplained poor vision is DUMP, which is a rare paraneoplastic disorder in which an underlying malignancy such as ovarian or pancreatic carcinoma causes bilateral blindness by uveal thickening, serous retinal detachment, and rapid cataract formation.[4] DUMP is possible in view of this patient's subsequent clinical course, which involved exudative detachment. The conversion of serous detachment to a rapidly progressive haemorrhagic detachment may have been influenced by treatment with warfarin or the presence of α-thalassaemia. However, it is noteworthy that there was minimal exudation during the initial fundal assessment of the patient's left eye 5 years previously.

Therefore, another hypothesis may be sought to explain the poor vision and similar bilateral fundal appearance following cataract surgery. CAR is a paraneoplastic process of photoreceptor degeneration, believed to be the remote effect of a primary malignancy — namely, photoreceptor toxicity caused by cross-reactive tumour antigen or retinotoxic tumour products.[5] Electroretinography may be non-recordable or show markedly reduced amplitudes.[6] The explanation for the poor vision in this patient's right eye may be the presence of subtle DUMP or CAR. CAR may have been the underlying cause of the initial photoreceptor dysfunction and poor vision.

Individuals with β-thalassaemia have been documented to display a mottled fundal appearance,[7] but visual impairment is not usually a feature. In this patient, direct invasion was unlikely to be due to the contralateral location of the primary tumour bulk because no direct invasion was visible on imaging. The exudative detachment may represent metastasis to the choroid, which is extremely rare in NPC.[8]

The bilaterality and similarity of fundal appearance in both eyes prior to the occurrence of the left haemorrhagic detachment and unexplained decrease in visual acuity support the finding of a paraneoplastic syndrome. Another point to consider is that despite similar fundal appearances, cataract surgery in her left eye preceded surgery in her right eye by 5 years. Although anaplastic tumours generally behave aggressively and progress within a short time, it is possible that the tumour began its paraneoplastic manifestations in the carcinoma in situ or early stages.[9] Furthermore, there is evidence that anaplastic tumours may develop from more benign forms of malignancy.[10]

This report describes a unique case of NPC presenting with paraneoplastic syndrome. The cause may initially have been CAR, but the condition progressed to DUMP and haemorrhagic detachment owing to systemic blood dyscrasia and anticoagulation.

References

1. Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. Trans Am Ophthalmol Soc 2003;101:53-56; discussion 56-57.
2. Schocket LS, Syed NA, Fine SL. Primary adrenal lymphoma with choroidal metastases. Am J Ophthalmol 2002;134:775-776.

3. Brink H, Deutman A, Beex L. Unusual retinal pigment epitheliopathy and choroidopathy in carcinomatosis: a rare case of cancer-associated retinopathy. Graefes Arch Clin Exp Ophthalmol 1997; 235:59-61.
4. O'Neal KD, Butnor KJ, Perkinson KR, Proia AD. Bilateral diffuse uveal melanocytic proliferation associated with pancreatic carcinoma: a case report and literature review of this paraneoplastic syndrome. Surv Ophthalmol 2003;48:613-625
5. Grunwald GB, Klein R, Simmonds MA, Kornguth SE. Autoimmune basis for visual paraneoplastic syndrome in patients with small-cell lung carcinoma. Lancet 1985;3: 658-661.
6. Matsui Y, Mehta MC, Katsumi O, Brodie SE, Hirose T. Electrophysiological findings in paraneoplastic retinopathy. Graefes Arch Clin Exp Ophthalmol 1992;230:324-328.
7. Sorcinelli R, Sitzia A, Figus A, Lai ME. Ocular findings in beta-thalassemia. Metab Pediatr Syst Ophthalmol 1990;13: 23-25.
8. Ozyar E, Kiratli H, Akbulut S, Uzal D, Atahan IL. Choroid metastasis of undifferentiated nasopharyngeal carcinoma. J Laryngol Otol 1998;112:667-669.
9. Teo P, Tai TH, Choy D. Nasopharyngeal carcinoma with dermatomyositis. Int J Radiat Oncol Biol Phys 1989;16:471-474.
10. Nikiforova MN, Kimura ET, Gandhi M, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab 2003; 88:5399-5404.

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Terminology for Angle Closure Glaucoma

From the 20th Asia Pacific Academy of Ophthalmology Congress, Kuala Lumpur, Malaysia, 27-31 March 2005

Dr T Aung
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Primary angle closure glaucoma (PACG) is an important cause of glaucoma worldwide, especially in Asia. PACG is estimated to affect 30 million people and causes more blindness than primary open angle glaucoma (POAG).

Traditionally, PACG has been classified according to whether the presentation is acute or chronic. Previous definitions include acute or symptomatic PACG, chronic or asymptomatic PACG, or intermittent or subacute PACG. A limitation of this system is lack of standardisation, and the system does not take into consideration the degree or consequences of angle obstruction or the presence of glaucomatous optic neuropathy. In addition, there may be overlap in the clinical presentation, as eyes with acute angle closure (AAC) may have underlying chronic disease and eyes with chronic disease may develop an acute episode.

In 1998, glaucoma specialists from around the world met to discuss the definitions used for glaucoma. The classification for PACG that was proposed was based on the presence of structural and functional consequences of angle closure, with emphasis on the presence of glaucomatous damage to the optic nerve, peripheral anterior synechiae (PAS), and raised intraocular pressure (IOP). Three new categories of angle closure were determined within this new classification, as follows:[1]

- narrow angle or primary angle closure suspect (PACS)
- primary angle closure (PAC)
- primary angle closure glaucoma (PACG).

In the first stage of PACS, there is no other abnormality other than angle closure. The term 'angle closure' is used when an observer cannot see the pigmented trabecular meshwork for a certain extent of the angle on indentation gonioscopy. The exact amount is arbitrary and has been quoted as 270°. However, recent studies have shown that this definition may be too strict and that 180°, or even 90°, may be the minimum phenotypic criterion to define angle closure.

For a definition of PAC, the presence of a narrow angle is combined with some consequence of the angle closure process such as PAS and/or raised IOP due to closure of the angle (defined as >2 standard deviations above the norm for the population studied).

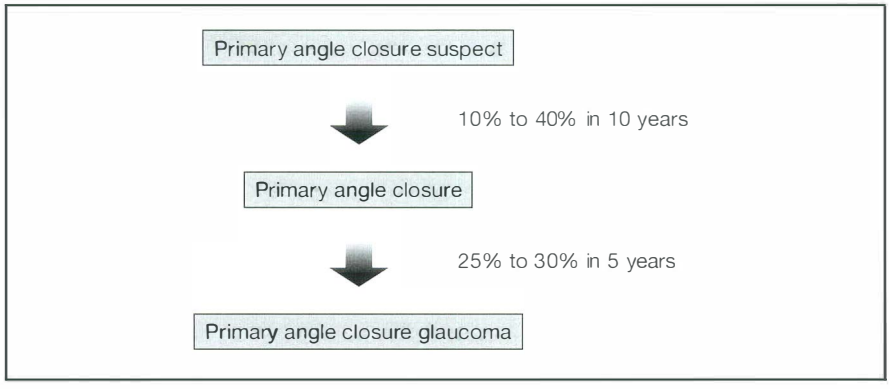
PACG is classified as a narrow angle in the presence of glaucomatous optic neuropathy outside the limits of the population studied, with or without visual field loss. This classification is analogous to POAG.

This new classification differentiates patients with true disease from suspects who are at increased risk for disease. The term 'glaucoma' is thus reserved for those who have injury to the optic nerve, judged by enlargement of the cup/disc ratio outside the limits for the population combined with visual field abnormality.

Limited evidence from epidemiological studies, many with small samples, suggests that the natural course of PACG begins with PACS, which may worsen to become PAC in approximately 10% to 40% of patients over 10 years, and further develop into PACG in approximately 25% to 30% of patients over 5 years (Figure 1).

An acute episode of angle closure is now termed acute or symptomatic PAC. This condition may occur at any stage during the disease and, if it results in glaucomatous damage, should be termed PACG.

Figure 1. Natural course of primary angle closure glaucoma.



Reference

1. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 2002;86:238-242.

Text prepared by a staff medical writer.

SEPTEMBER 2005

7-10
16th World Congress of the International Society for Laser Surgery and Medicine (ISLSM)
Tokyo, Japan
Contact: Prof Harubumi Kato
Tel: (81 332) 636 474
Fax: (81 332) 637 537
E-mail: islsm2005@cs-inc.co.jp

10-14
XXII Congress of the ESCRS (European Society of Cataract & Refractive Surgeons)
Lisbon, Portugal
Tel: (353) 1209 1100
Fax: (353) 1209 1112

25-29
15th Congress of the European Society of Ophthalmology (SOE) & Joint Meeting with 103rd Annual Meeting of the German Society of Opthalmology (DOG)
Berlin, Germany
Contact: Porstmann Kongresse GmbH
Tel: (49 302) 844 990
Fax: (49 328) 449 911
E-mail: soe2005@porstmann-kongresse.de

OCTOBER 2005

15-18
Annual Meeting of the American Academy of Ophthalmology
Chicago, IL, USA
Contact: Anna Zammataro, American Academy of Ophthalmology, PO Box 7424, San Francisco, CA 94120-7424, USA
Tel: (1 415) 561 8500
Fax: (1 415) 561 8533
E-mail: meetings@aao.org

NOVEMBER 2005

28-1 December
2005 Joint Philippine Academy of Ophthalmology and American Academy of Ophthalmology Meeting
Manila, The Philippines
Contact: Mr Zosimo R Garcia, Philippine Congress Organizing Center, 2nd Floor, Physicians' Tower, 533 United Nations Avenue, Ermita, 1000 Manila, The Philippines
Tel: (63 2) 521 4884/526 8105
Fax: (63 2) 522 1090
E-mail: pcoc@manila-online.net
Website: www.pao.org.ph

DECEMBER 2005

Hong Kong Ophthalmological Society Meeting
Hong Kong, China
Tel: (852) 2761 9128,
Fax: (852) 2715 0089
E-mail: info@hkos.org.hk

FEBRUARY 2006

19-24
World Ophthalmology Congress
XXX International Congress of Ophthalmology
XXVI Panamerican Congress of Ophthalmology
XVII Brazilian Congress of Prevention of Blindness
São Paulo, Brazil
Contact: Congress Secretariat, Rua Cel. Joaquim Ferreira Lobo, 244, 04544-150 São Paulo – SP, Brazil
Tel: (55 11) 3849 0379
Fax: (55 11) 3845 6818
E-mail: info@ophthalmology2006.com.br
Website: www.ophthalmology2006.com.br

MARCH 2006

18-22
American Society of Cataract and Refractive Surgery
San Francisco, CA, USA
Tel: (1 703) 591 2220
Fax: (1 703) 591 0614
E-mail: ascrs@ascrs.org
Website: www.ascrs.org

Future ASCRS/ASOA Meetings
2007 — San Diego, CA, USA, 28 April-2 May
2008 — Chicago, IL, USA, 12-16 April
2009 — San Francisco, CA, USA, 4-8 April
2010 — Washington, DC, USA, 10-14 April

APRIL 2006

30-5 May
Association For Research In Vision & Ophthalmology (ARVO)
Fort Lauderdale, FL, USA
Website: www.arvo.org

Note to Readers
This page is intended to highlight activities of interest to glaucoma specialists and ophthalmologists in Asia. Please let us know of any forthcoming activities that you may be organising or wish to feature on this page.

Future ARVO Meetings
Fort Lauderdale, FL, USA
2007 — 6-10 May
2008 — 27 April-1 May
2009 — 3-7 May
2010 — 2-6 May

MAY 2006

18-22
Annual Symposium and Congress of the American Society of Cataract and Refractive Surgery
San Francisco, CA, USA
Contact: ASCRS-ASOA, 4000 Legato Road, Suite 850, Fairfax, Virginia 22033, USA
Tel: (1 703) 591 2220
Fax: (1 703) 591 0614

25-28
International Congress on Glaucoma Surgery
Toronto, Canada
Contact: Continuing Medical Education Office
Tel: (1 416) 978 2719
Fax: (1 416) 946 7028

AUGUST 2006

16-18
11th International Myopia Conference
Singapore
Contact: Colleen Koh
Tel: (65) 6435 3670
Fax: (65) 6438 9757

Next SEAGIG Meeting
The next SEAGIG/AOGS meeting will be held in Chennai, India, in 2006, in conjunction with the Glaucoma Society of India. The details have yet to be confirmed. See this page for further information.

TEACHING COURSE ON RETINAL AND VITREOUS SURGERY

Workshop with International Faculty
30-31 October 2005
Hangzhou, China
Scientific organisation: Prof Ingrid Kreissig
E-mail: ingrid.kreissig@augen.ma.uni-heidelberg.de
Local contact: Prof Jing Wang
Tel: (86 571) 8721 4083; *Fax:* (86 571) 8721 4128; *E-mail:* zyec@mail.hz.zj.cn

WORLD OPHTHALMOLOGY CONGRESS

The World Ophthalmology Congress, comprising the XXX International Congress of Ophthalmology, the XXVI Panamerican Congress of Ophthalmology, and the XVII Brazilian Congress of Prevention of Blindness, is to be held in São Paulo, Brazil, from 19-24 February 2006.

The scientific programme is very attractive to ophthalmologists from around the world, as it embraces international specialty issues, with special attention to the state of the art in ophthalmology. Programme highlights will include Symposia and Sessions with themes, Courses, Workshops, Video Presentations, Posters, and Free Papers.

More than 4000 scientific presentations will be delivered by more than 2500 speakers. The programme includes the most comprehensive update on new trends, with special emphasis on the results of recent clinical trials and their current and potential impact on patient care. Hundreds of educational opportunities have been designed to help ophthalmologists deliver the very best care to patients.

To help navigate the congress programme, the sessions have been organised around several main topics, coordinated by the world's best experts. Such topics include cataract, contact lens and refraction, external disease and the cornea, eye trauma, glaucoma, neurophthalmology, oculoplasty, oncology, paediatric ophthalmology, refractive surgery, the retina, uveitis, gene therapy, new technology, and blindness prevention.

As well as the main programme, subspecialty 1-day immersion programmes, led by some of the world's top ophthal-mologists, have been organised for cataract, retina, glaucoma, and refractive surgery. Each subspecialty day has a unique format and programme tailored to fit its subspecialty focus.

The World Forum of Non Profit Organization in Vision and Prevention of Blindness and the World Forum of Ophthalmological Journal Editors are also important additions to the main programme.

The social side should not be forgotten, as the congress takes place immediately before the Carnival, so stay an extra few days and enjoy the festival atmosphere and the Brazilian hospitality.

What the Experts Say

"*Ophthalmology has a history of leadership in Medicine. The 30th International Congress of Ophthalmology in Brazil establishes another first, linking an International Congress with a regional Congress (PAAO) and a very large National Congress. The social and intellectual opportunities are enormous.*" — Bruce E Spivey

"*ICO is always an excellent occasion in which we can see the latest development of science and technology in ophthalmology.*" — Dennis SC Lam

"*I look forward to an opportunity of exciting scientific clinical exchange, the warm hospitality of the Brazilians and the camaraderie of ophthalmologists from all over the world.*" — Mark OM Tso

"*Professor Rubens Belfort has put together a forceful team of organizers to plan a truly superb meeting. ... we will be able to come together, to hear the latest information in plenary sessions, scientific and clinical presentations, courses, and symposia, to cross-fertilize with our colleagues from around the world, to see old friends and make new ones, all united in the wish to bring ophthalmology to the highest state of the art throughout the globe and to fight together against blindness.*"— Robert Ritch

"*The scientific programme features the leading ophthalmologists of the world, and is going to be exciting and enlightening with the state of the art in ophthalmology.*" — S Selvarajah

For further information, visit the website at: www.ophthalmology2006.com.br/support.php

Asian Journal of OPHTHALMOLOGY is the official publication of the South East Asia Glaucoma Interest Group, and is a peer-reviewed quarterly publication for the practising ophthalmologist. The Journal is indexed in EMBASE/Excerpta Medica.

The Journal welcomes contributions within the categories of original research, invited papers, review articles, case reports, conference reports, and letters to the editor. Submissions may be sent by e-mail or on disk to the following address:

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Asian Journal of OPHTHALMOLOGY
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Manuscript Criteria

Submitted manuscripts should adhere to the stated format. Manuscripts that do not conform to the approved format will be returned without review. Authors should refer to the latest version of the *Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication* for guidance.[1]

A covering letter stating that the submitted material has not been previously published and is not under consideration for publication elsewhere should be included. The receipt of submissions will be acknowledged. All accepted papers become the permanent property of Asian Journal of OPHTHALMOLOGY and may not be published elsewhere without written permission from the Journal.

Manuscript Preparation

The manuscript must be accompanied by a title page, an abstract, and key words. The title page must contain the title of the manuscript; a short running title (no more than 40 characters, including spaces); the full names of all authors and their 2 highest qualifications; the department(s) and institution(s) to which each author is affiliated; and the full name, address, telephone and fax numbers, and e-mail address of the corresponding author. The abstract for original articles must be structured with the following subheadings: Aim(s), Patients and Methods, Results, and Conclusion(s). Abstracts for all other articles must be unstructured. Abstracts should be no longer than 250 words. The key words must be Medical Subject Headings taken from Medline/*Index Medicus*.

Tables and Figures must be cited in the text in numerical order. Tables and Figures must be submitted in separate electronic files and clearly labelled with a legend. The resolution of Figures must be at least 350 dpi. When symbols, arrows, numbers, or letters are used to identify part of an illustration, each one should be identified and clearly explained in the legend. If only hard copies of Figures are submitted, each one should have a label pasted on the back indicating the number of the Figure, the author's name, and the top of the Figure (Figures must not be written on and paper clips must not be used). Abbreviations should be avoided in Tables. If abbreviations are necessary, they must be explained in a footnote. Footnotes for Figures and Tables must use the following symbols, in this order: *, †, ‡, §, ‖, ¶, **, ††, ‡‡, §§, ‖‖, ¶¶.

References must be cited in superscript in numerical order in the text. References should follow the *Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication*.[1] The accuracy of the references is the responsibility of the authors. Journal titles should be abbreviated in accordance with Medline/*Index Medicus*. The following are examples of reference style:

Standard journal article

Cheung JC, Wright MM, Murali S, Pederson JE. Intermediate-term outcome of variable dose mitomycin C filtering surgery. Ophthalmology 1997;104:143-149.

Supplement

Taylor A, Jacques PF, Epstein EM. Relations among aging, antioxidant status, and cataract. Am J Clin Nutr 1995;62 (6 Suppl): 1439-1447.

Books and other monographs

Kupfer C, Underwood B, Gillen T. Leading causes of visual impairment worldwide. In: Albert DM, Jakobiec FA, editors. Principles and practice of ophthalmology. Philadelphia: WB Saunders Company; 1994: 1250-1251.

The following style should be used:

- all papers must be written in English; spelling should comply with the Concise Oxford English Dictionary
- Arabic numerals should be used for all numbers, except for numbers below 10 at the beginning of sentences, which should be spelled out
- abbreviations should not appear in the title or abstract and their use in the text should be limited; abbreviations should be defined at the first mention in the text unless they are standard units of measurement
- Système International (SI) measurements must be used for all laboratory values
- generic drug names must be used unless the specific trade name of a study drug is directly relevant to the discussion.

Reference

1. International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. ICMJE; 2004. www.icmje.org

The full version of the Information for Authors is available at:
www.seagig.org

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1-drop-daily XALACOM provides your patients with

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- ***Tolerability that supports therapeutic goals***
- ***Added power without the added drops***

XALACOM is indicated for the reduction of IOP in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to topical beta-blockers.

XALACOM is contraindicated in patients with reactive airway disease, including bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- or third-degree atrioventricular block; overt cardiac failure; cardiogenic shock; or hypersensitivity to any component of this product.

XALACOM has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation and growth of eyelashes. The iris pigmentation changes may be permanent.

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Please refer to product insert for full prescribing information.

References:
1. Higginbotham EJ, Feldman R, Stiles M, Dubiner H, for the Fixed Combination Investigative Group. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. *Arch Ophthalmol*. 2002;120:915-922. 2. Data on file. Pfizer Inc, New York, NY.

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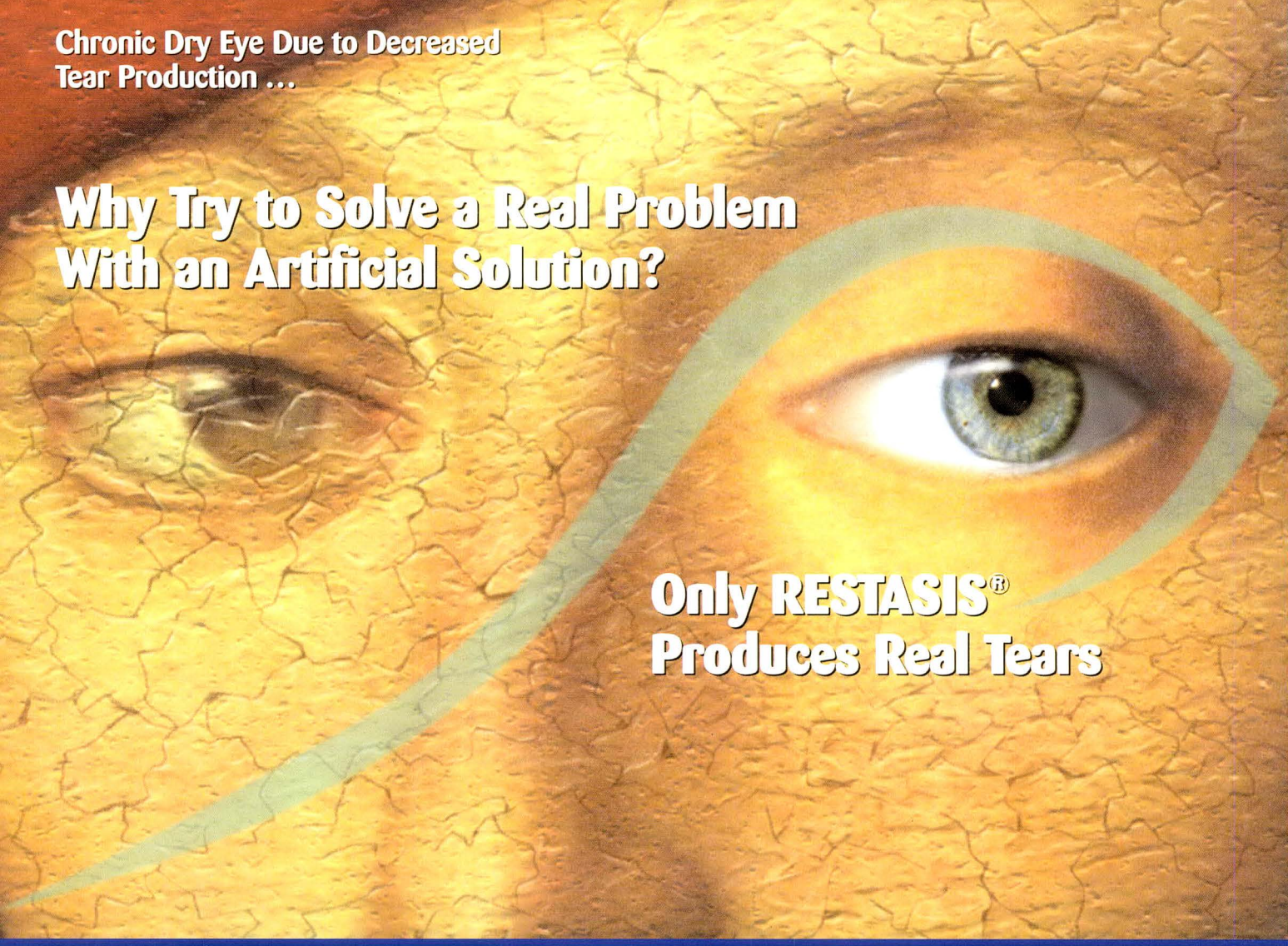

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Important Safety Information

RESTASIS® is contraindicated in patients with active ocular infections and has not been studied in patients with a history of herpes keratitis.

The most common adverse event was ocular burning (upon instillation)—17%. Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

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References: 1. Sall K, Stevenson OD, Mundorf TK, Reis BL, and the CsA Phase 3 Study Group. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology.* 2000;107:631-639. **2.** RESTASIS® (cyclosporine ophthalmic emulsion) [prescribing information]. Irvine, Calif.: Allergan, Inc.; Rev. 2/04.

For more information, please visit our Web site, www.restasis.com.

Restasis® B.I.D.
(Cyclosporine Ophthalmic Emulsion) 0.05%

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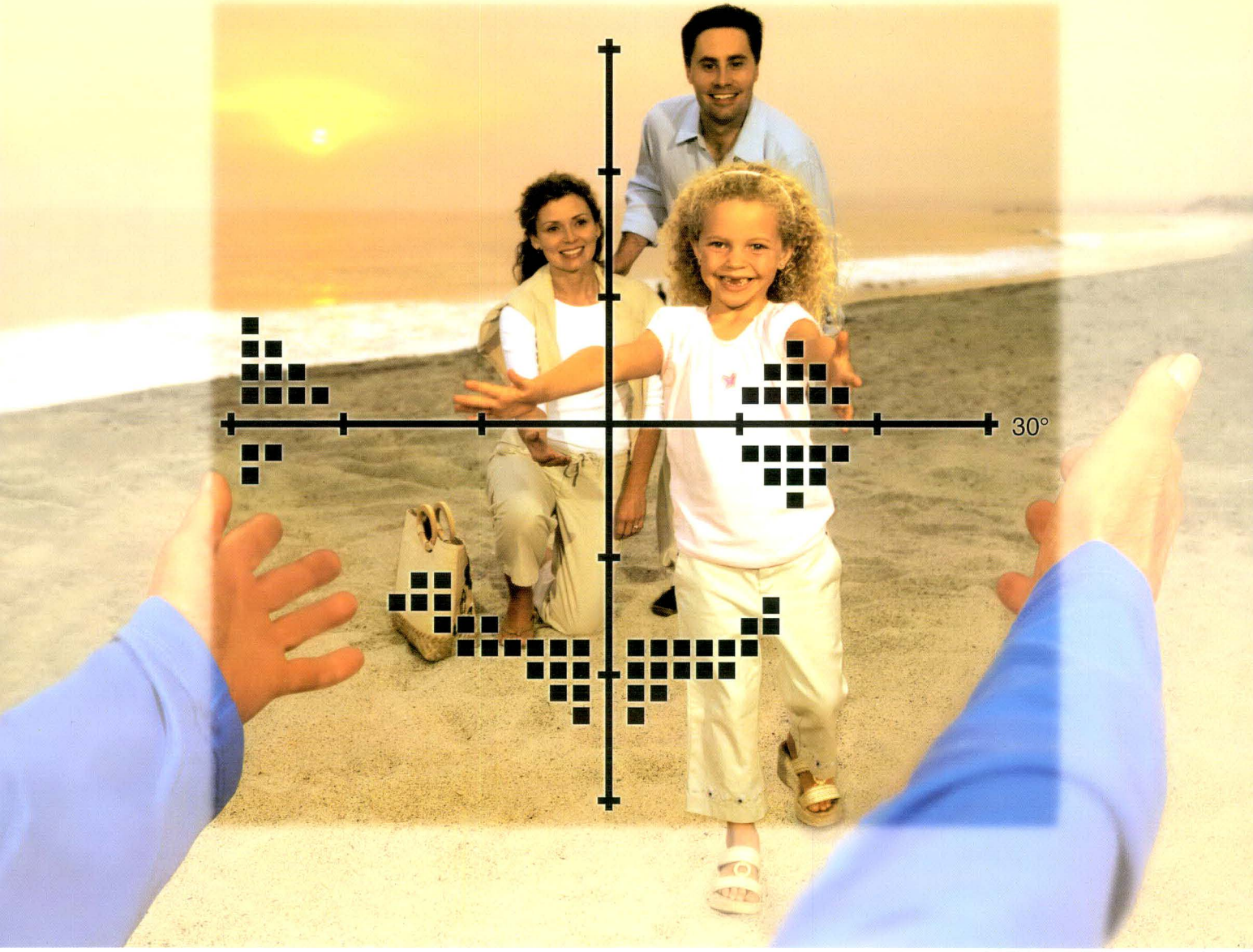

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