·Clinical Research·

Study of long term structural and functional changes in medically controlled glaucoma

Achyut N Pandey[1], *S Sujata*[2]

[1]Department of Ophthalmology, VCSG Medical College and Research Institute, Srinagar Garhwal, Uttarakhand 246174, India

[2]Joseph Eye Hospital, Trichy, Tamilnadu 426001, India

Correspondence to: Achyut N Pandey, Department of Ophthalmology, VSCG Medical College and Research Institute, Srinagar Garhwal,Dist Pauri Garhwal, Uttarakhand 246174, India. achyutpandey@gmail.com

Received: 2013-08-28 Accepted: 2013-11-25

Abstract

• AIM: Prospectively analyze the long term structural and functional changes in patients of primary open angle glaucoma (POAG) receiving medical therapy (beta blockers and non beta blockers). In this study an attempt has been made to evaluate whether medical reduction of IOP prevents or delays the progression of glaucomatous visual field loss and/or optic nerve damage in patients with open angle glaucoma.

• METHODS: Study conducted over a period of 27 months, at a tertiary eye care hospital including both eyes of 40 patients with POAG. Group 1 (20 patients, 40 eyes) received beta-blockers, and Group 2 (20 patients, 40 eyes) received non-beta-blockers. Each patient underwent intraocular pressure measurement, best corrected visual acuity, slit-lamp, fundus examination, gonioscopy, central corneal thickness, visual field assessment by Humphrey automated perimetry and retinal nerve fibre layer thickness by Stratus optical coherence tomography at baseline and at two subsequent visits. The average time interval between each visit was 10-11 months. The statistical analysis was done using one-way analysis of variance (ANOVA). Post-hoc test, using tukey´ method were adopted. Probablity (*P*) value of 0.05 or less was considered to be statistically significant.

• RESULTS: A total of 80 eyes of 40 patients of POAG were enrolled, 24 males, 16 females, age group 50-80 years. In both beta and non beta blocker group, reduction (improvement) in mean IOP from initial levels to the levels achieved at the 2nd and 3rd visits was statistically significant. One way ANOVA (df=2), fisher *f* value=11.64, *P*=0.000, one way ANOVA (df=3), fisher *f* value=35.61, *P*=0.000. Both mean deviation (MD) and pattern standard deviation (PSD) in both beta and non beta blockers at different visits were not statistically significant. Retinal nerve fibre layer thickness (RNFL) - only mean inferior retinal nerve fibre layer, the difference between the mean value in beta and non beta blocker groupwere statistically significant. [unpaired *t* test value (df=78) =2.27, *P*=0.03]. Side effects with beta blocker were conjunctival hyperemia (10%), burning (5%), and conjunctival hyperemia (5%) in non beta blockers.

• CONCLUSION: Non-beta-blockers are as effective as beta-blockers in bringing about a significant lowering of intraocular pressure to the normal range, and in preventing progressive damage to the visual fields and retinal nerve fibre layer. The absence of systemic side effects and superior IOP lowering efficacy has made non beta-blockers attractive for first line therapy for the treatment of glaucoma worldwide.

• **KEYWORDS:** optical coherence tomography; retinal nerve fibre layer; mean deviation; pattern standard deviation

DOI:10.3980/j.issn.2222-3959.2014.01.24

Pandey AN, Sujata S. Study of long term structural and functional changes in medically controlled glaucoma. *Int J Ophthalmol* 2014;7 (1):128-132

INTRODUCTION

Glaucoma is a progressive optic neuropathy characterized by structural changes of optic nerve and retina that are associated with the development of defects in visual function. The loss of retinal ganglion cells in glaucoma can be reflected structurally as a localized or diffuse thinning of the retinal nerve fiber layers and its measurements have been co-related with functional change in visual field[1].

The accurate identification of true glaucomatous progression is an ongoing challenge in clinical practice and research. Identifying progression by functional means is difficult because visual fields that appear to have deteriorated over a period of follow up may improve at subsequent visits. It is difficult to separate true glaucomatous progression from transient fluctuations in the visual field that result from learning effects, fatigue physiological state of eye and from long term fluctuations that is inherent to the disease[2].

Management of patients suffering from glaucoma includes: periodic IOP estimation and evaluation of disc and field changes. The main thrust of medical management of

glaucoma is aimed at achieving sustained IOP levels below the target pressure.

Beta blockers lower the IOP by decreasing the aqueous production. It does not have any significant intrinsic sympathomimetic or membrane stabilizing activity. However blocking the beta receptors in reduction of intracellular second messenger cyclic AMP is believed to be involved in aqueous humour dynamics.

Prostaglandins are a relatively recent class of drugs added to the armamentarium of glaucoma medications. It was initially suggested that prostaglandins reduce IOP by increasing uveoscleral outflow since no effect was found on fluorophotometrically measured aqueous flow or on topographical outflow. It was later seen that uveoscleral outflow increases because of relaxation of ciliary body muscle and dilated spaces between ciliary muscle bundles; in addition to altered metabolism of the extracellular matrix that surrounds the ciliary muscle cell.

In this study, an attempt has been made to evaluate whether medical reduction of IOP prevents or delays the progression of glaucomatous visual field loss and/or optic nerve damage in patients with open angle glaucoma. Objective quantitative measurement of retinal nerve fibre layer (RNFL) thickness, as measured by optical coherence tomography (OCT), will be correlated with the quantitative measurement of visual fields in patients on long term medical therapy[3-5].

To prospectively analyze the long term structural and functional changes in patients of primary open angle glaucoma (POAG) receiving medical therapy (beta blockers and non beta blockers).

SUBJECTS AND METHODS

The present study was a prospective study involving both eyes of 40 patients with primary open-angle glaucoma who attended the Glaucoma Clinic of the Institute of Ophthalmology, Joseph Eye Hospital, Tiruchirapalli, India. These patients were all on medical treatment with beta-blockers or non-beta-blockers during the entire duration of the study along the follow-up period 27 months. The average time interval between each follow up visits was 10-11 months. The study was approved by the Institutional Review Board. Each eligible patient provided informed consent prior to enrolment in the study.

At presentation and at subsequent follow-up visits, examination of the following parameters was undertaken-

1) Refraction and determination of the best corrected visual acuity (BCVA);

2) Anterior segment examination by slit-lamp biomicroscopy;

3) Measurement of the IOP by Goldmann appalanation tonometry, gonioscopy;

4) Fundus examination;

a) Stereoscopic examination of optic nerve head using 78D lens;

b) for examination of periphery of the fundus by indirect ophthalmoscopy;

5) Measurement of central corneal thickness;

6) Analysis of the visual field using the Humphrey Field Analyser (HFA 30-2);

7) Analysis of retinal nerve fibre layer thickness by OCT.

Inclusion Criteria Patients were included in the study if they satisfied the following requirements:

1) BCVA better than 20/40;

2) Medically well controlled IOP (target pressure) throughout the period of follow up;

3) Presence of characteristic glaucomatous cupping, which is focal rim notching, rim thinning, excavation of rim, retinal nerve fibre layer defects;

4) characteristic glaucomatous field defects;

5) minimal or no lens changes;

6) OCT images by the fast RNFL protocol.

Exclusion Criteria Patients were excluded from the study if any one of the following was noted: BCVA less than 20/40.

1) Corneal or lenticular opacity that interfered with clinical evaluation of the optic disc;

2) Significant peripapillary atrophy interfering with examination;

3) Prior surgery or laser procedures;

4) Past history of neurological diseases;

5) Patient had a tilted disc or with vitreous or retinal diseases; Patient was unable to perform field or to undergo OCT.

Visual field examinations were performed with the Humphrey Field Analyser 30-2 program, (Allergan-Humphrey Inc, San Leandro, California, USA)[6]. The criteria for visual field abnormalities on the computerized perimetric tests included a pattern standard deviation (PSD) with a P value less than 0.05 or a glaucoma hemifield test outside normal limits obtained with at least 3 sequential and reproducible visual field examinations. A fixation loss of less than 20% and false positive and false- negative rates less than 33% were the criteria for reliable visual fields.

Optical coherence tomography were performed in all patients using Fast RNFL Thickness protocol and Fast Disc photograph by time domain OCT (stratus OCT)[7,8]. Three circular scans were obtained for each eye at a diameter of 3.4mm around the optic disc. In each eye, average RNFL thickness measurements were obtained in temporal, superior, nasal, and inferior quadrants. A single index of average RNFL thickness throughout 360° also was obtained.

Statistical Analysis The statistical analysis was done using one-way analysis of variance (ANOVA) for intergroup comparison, Post-hoc test, using Tukey's method were adopted. Fisher f value was calculated for initial and final visits by using ANOVA. Probablity (P) value of 0.05 or less was considered to be statistically significant. Statistical analysis was done by calculating initial and final visit.

Table 1 Variations in mean intraocular pressure (IOP) in eyes of patients with POAG

Patient treatment group	Mean IOP (mmHg) at initial visit	Mean IOP (mmHg) at second visit	Mean IOP (mmHg) at final visit	Fisher *f* value (*P*)
Beta-blockers	21.28±4.44	18.73±3.2	17.4±3.18	11.64 (*P*=0.000)
Non-beta-blockers	24.33±4.99	18.63±4.71	16.78±2.26	35.61 (*P*=0.000)

Table 2 Variations in mean CDR in patients with POAG

Patient treatment group	Mean CDR at initial visit	Mean CDR at second visit	Mean CDR at final visit	Fisher *f* value (*P*)
Beta blockers	0.70±0.15	0.715±0.15	0.710±0.15	0.106(*P*=0.90)
Non beta- blockers	0.76±0.13	0.76±0.13	0.76±0.13	0.00 (*P*=0.00)

Table 3 Variations in mean values of MD in patients with POAG

Patient treatment group	Mean MD at initial visit	Mean MD at second visit	Mean MD at final visit	Fisher *f* value (*P*)
Beta blockers	-9.12±8.38	-9.19±8.37	-8.91±8.45	0.012 (*P*=0.988)
Non beta blockers	-11.31±9.2	-11.56±8.9	-10.65±8.6	0.112 (*P*=0.89)

Table 4 Variations in mean values of PSD in eyes of patients with POAG

Patient treatment group	Mean PSD at initial visit	Mean PSD at second visit	Mean PSD at final visit	Fisher *f* value (*P*)
Beta-blockers	6.35±3.74	6.01±3.92	6.05±4.04	0.091 (*P*=0.913)
Non-beta-blockers	6.64±4.27	7.07±3.96	7.01±4.2	0.126 (*P*=0.882)

RESULTS

The present study was conducted at the Glaucoma Department of the Institute of Ophthalmology, Joseph Eye Hospital, Tiruchirapalli (Tamil Nadu) over a period of 27 months (September 2009 to December 2011).

Forty patients (80 eyes) of primary open angle glaucoma were enrolled in the study. The patients (24 males and 16 females, ranging in age from less than 50 years to 80 years) were divided into two groups depending on the treatment received: group 1 (20 patients), who received beta-blockers, and group 2 (20 patients) who received non-beta- blockers.

Twenty patients (40 eyes) received beta-blockers as treatment for primary open-angle glaucoma who ranged in age from 51 to 80 years (mean age 63.9±5.4 years).

Twenty patients (40 eyes) received non beta-blockers as treatment for primary open-angle glaucoma who ranged in age from less than 50 years to 80 years (mean age 60.85±9.2 years). Out of 20 patients who were on non beta-blockers, eight were on latanoprost, six on bimatoprost three on travoprost and three on brimonidine.

The reduction (improvement) in mean IOP from initial levels to the levels achieved at the second and third visits was statistically highly significant in both the groups.

With regard to mean IOP, a statistically highly significant reduction was achieved in both treatment groups over the course of the study, as assessed at three visits (initial, second and final) (Table 1). The percentile reduction in IOP was 12.18% in the beta- blocker group and 18.87% in the non-beta-blocker group.

The observations on reduction of IOP made in the present study are consistent with those of previous studies, which have shown better IOP lowering efficacy of non-beta-blockers, such as latanoprost. The difference between the mean CDR values at different visits was not statistically significant in both the groups.

With reference to measurements of the mean cup: disc ratio (CDR) in the present study, in both beta blocker and non beta blocker group, no statistically significant differences were observed (Table 2). These results suggest that the treatment given, whether beta-blockers or non-beta-blockers also prevented deterioration in the mean CDR values by arresting progression of glaucoma.

The difference between the mean mean deviation (MD) values at different visits was not statistically significant in both the groups. The difference between the mean PSD values at different visits was not statistically significant in both the groups.

With reference to measurement of the mean MD and mean PSD values in the present study, in both treatment groups, no statistically significant differences were observed between the mean values noted at the initial, second and final visits (Tables 3, 4). These results suggest that both beta-blockers and non-beta-blockers were equally effective in preventing worsening of the mean MD and mean PSD values by arresting progression of glaucoma.

The difference between the mean average RNFL values at different visits was not statistically significant in both the groups (Table 5).

In the present study, measurements of RNFL thickness were made for superior, inferior, nasal and temporal RNFL, and the average RNFL thickness was also derived. In both treatment groups, no statistically significant differences were observed between the mean values of superior, inferior, nasal, temporal and average RNFL thickness recorded at the initial, second or final visits. These results suggest that both beta- blockers and non-beta-blockers were effective in

Table 5 Variations in mean values of average retinal nerve fibre layer (ARNFL) thickness in eyes of patients with primary open angle glaucoma

Patient treatment group	Mean ARNFL thickness (μm) at initial visit	Mean ARNFL thickness (μm) at second visit	Mean ARNFL thickness (μm) at final visit	Fisher *f* value (*P*)
Beta blockers	75.78±16.495	74.93±17.06	74.21±17.06	0.087 ((*P*=0.917)
Non beta blockers	72.15±17.1	69.87±18.9	72.16±18.4	0.211 (*P*=0.81)

Table 6 Variations in mean inferior retinal nerve fibre layer (IRNFL) thickness in eyes of patients with primary open angle glaucoma

Patient treatment group	Mean IRNFL thickness (μm) at initial visit	Mean IRNFL thickness (μm) at second visit	Mean IRNFL thickness (μm) at final visit	Fisher *f* value (*P*)
Beta blockers	90.7±30.82	89.0±30.54	87.9±30.9	0.084 (*P*=0.92)
Non beta blockers	78.6±26.6	78.6±26.6	73.85±23.98	0.454(*P*=0.64)

Table 7 Variations in mean IRNFL thickness in eyes of patients with primary open angle glaucoma:unpaired *t* test value

Initial visit *t* value	Second visit *t* value	Final visit *t* value
(d.f.=78) 1.88 (*P*=0.06) not significant	(d.f.=78) 1.62 (*P*=0.10) not significant	(d.f.=78) 2.27 (*P*=0.03) significant

preventing worsening of the mean values of superior, inferior, nasal, temporal and average RNFL thickness across all visits by arresting progression of glaucoma.

Statistical Analysis a) Differences between mean IRNFL at different visits (calculated by one-way analysis of variance [ANOVA], degree of freedom.=2) (Tables 6,7). b) Post hoc testing by Tukey's HSD not done because Fisher F value was not significant. c) Differences between mean IRNFL in beta-blocker group *vs* mean. IRNFL in non-beta-blocker group (calculated by unpaired *t* test).

These authors found that the rate of RNFL thinning was variable among patients with glaucoma, with an increased rate of loss in patients with a higher baseline RNFL thickness.

In the present study, no dropouts were seen in both beta and non beta-blocker groups.

DISCUSSION

Glaucoma is an optic neuropathy characterized by specific and progressive injury to the optic nerve head and RNFL. Since IOP is a causal risk factor for glaucoma, lowering IOP aggressively reduces the risk of development of glaucoma and helps to delay and minimize its progression[17]. Assessing the amount of glaucomatous damage is the first step towards the correct management of glaucoma. The damage is usually estimated by observation of RNFL and optic disc, and by testing visual function by perimetry[18].

IOP is the critical factor influencing the progression of glaucomatous optic nerve damage. Large scale multicenter studies, including the Advanced Glaucoma Intervention Study the Collaborative Initial Glaucoma Treatment Study and Early Manifest Glaucoma Trial have shown that reduction of IOP is effective in countering the progression of glaucoma[3,9].

Observations made in the Early Manifest Glaucoma Trial suggested that the magnitude of initial IOP reduction was a major factor influencing outcome[9].

The observations on reduction of IOP made in the present study are consistent with those of previous studies, which have shown better IOP lowering efficacy of non-beta-blockers, such as latanoprost. Kahiwagi *et al*[10], in their study, noted a 35% fall in IOP in patients using latanoprost. Hedman *et al*[11] found a reduction of about 30%. Rao *et al*[15] stated that in the early stages of glaucoma ,the rate of progression worsened as the severity increased but in later stages rate of progression became smaller as the severity increased.

According to Ishibashi *et al*[12], latanoprost seemed to lead to a fairly uniform circadian reduction in IOP, whereas timolol seemed to be less effective during the night hours[13].

In case of CDR in the present study (Table 2), the results suggest that the treatment given, whether beta-blockers or non-beta-blockers also prevented deterioration in the mean CDR values by arresting progression of glaucoma.

Kaushik *et al*[14] observed that optic discs with larger vertical CDR and thinner RNFL had lower MD values in ocular hypertension whereas in glaucoma suapects ,small sized discs had thinner RNFL and lower values of MD.

In case of mean MD and mean PSD values in the present study (Tables 3, 4), the results suggest that both beta-blockers and non-beta-blockers were equally effective in preventing worsening of the mean MD and mean PSD values by arresting progression of glaucoma.

According to Leung *et al*[16], OCT glaucoma progression analysis offers a new approach to augment glaucoma progression analysis.In the present study, mean RNFL thickness for superior, inferior, nasal , temporal and average RNFL thickness (Tables 5, 6) were not significant in both the groups, suggest that both beta- blockers and non-beta-blockers were effective in preventing worsening of the mean values of superior, inferior, nasal, temporal and average RNFL thickness across all visits by arresting progression of glaucoma.

Studies have shown increased pigmentation of the iris, hypertrichosis, hyperemia, allergic contact dermatitis and cystoid macular edema with the use of latanoprost. A 10% incidence of conjunctival hyperemia was noted by Russo *et al*[19]

in their study. Noted adverse ocular and systemic effects of timolol, which included corneal punctate erosions, burning sensation, hyperemia, tear film alterations and corneal anesthesia and systemic effects included worsening of chronic obstructive pulmonary disease, heart blocks, central nervous system dysfunction and alteration of plasma lipid profile. In the present study, the following adverse effects were noted: conjunctival hyperemia in one of 20 (5%) patients in the non-beta-blocker group; hyperemia in two of 20 (10%) and burning in one of 20 (5%) patients in the beta-blocker group and no systemic side effects in both groups. These side effects as not serious enough to withdraw the drug, were treated with antibiotic eye drops.

In the present study, none of the patients in the non beta-blocker group showed iris pigmentation, iris cysts, cystoid macular edema or any other systemic side effects. In a study done by Thomas *et al* [20] side effects other than conjunctival hyperemia (15.4%) were minimal.

Although initial medical therapy for most glaucoma patients remains the gold standard, the question of the first line drug is an ongoing debate, which has been compounded by the new and effective class of drugs- prostaglandin analogues, Latanoprost for IOP lowering efficacy.

The results of the present study suggest that non-beta-blockers are as effective as beta-blockers in bringing about a significant lowering of intraocular pressure to the normal range (a target value below 18mmHg) and in preventing progressive damage to the visual fields and retinal nerve fibre layers. The absence of systemic side-effects and the feature of putative superior IOP-lowering efficacy make non-beta-blockers an attractive option for first-line therapy for the treatment of glaucoma. Further studies are recommended, wherein a larger sample size of patients, followed up over a longer duration, would help in confirming the initial results provided by the present study and in evaluating progression of glaucoma in patients on medical management.

ACKNOWLEDGEMENTS

The author thanks Dr. Amjad Salman, JEH, Trichy, Dr. BC Pandey, Dr. Preeti Pant and Divyam Pandey for their help.

Conflicts of Interest: Pandey AN, None; **Sujata S**, None.

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