CLINICAL STUDY

# The comparative ocular hypotensive effect of apraclonidine with timolol maleate in exfoliation versus primary open-angle glaucoma patients

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**Abstract**

*Purpose* **To compare the effect of adding apraclonidine 0.5% to timolol maleate 0.5% in patients with exfoliation versus primary open-angle glaucoma. Since exfoliation glaucoma is known to demonstrate higher pressures than primary open-angle glaucoma on timolol maleate therapy alone, the authors wished to determine whether apraclonidine equalised the intraocular pressure (IOP) between these two glaucomas when added to timolol maleate.**

*Methods* **We age-matched 30 consecutive exfoliation and 30 primary open-angle glaucoma patients who had an IOP $\geqslant$ 22 mmHg on timolol maleate alone. Patients underwent IOP diurnal curve testing on timolol maleate twice daily alone and, 2 months later, following the addition of apraclonidine 0.5% three times daily. Statistical analysis of the IOP at each time point was by an unpaired *t*-test between groups. A paired *t*-test was used to evaluate the reduction in IOP from baseline within groups after the addition of apraclonidine.**

*Results* **On timolol maleate alone, exfoliation patients had a higher mean IOP at 06:00 and 10:00 hours as well as a higher peak, range and standard deviation of the IOP compared with primary open-angle glaucoma patients ($p < 0.05$). Following the addition of apraclonidine the mean, peak and range of IOP were statistically similar between groups and only the standard deviations remained higher in the exfoliation glaucoma group ($p < 0.001$). The mean diurnal IOP after apraclonidine was added was 20.5 $\pm$ 7.0 mmHg in the exfoliation glaucoma group and 20.0 $\pm$ 3.4 mmHg in the primary open-angle glaucoma group, which was not significantly different between groups ($p = 0.73$).**

*Conclusions* **This study suggests that apraclonidine 0.5% used adjunctively with timolol maleate 0.5% solution is associated generally with similar IOP control in exfoliation and primary open-angle glaucoma patients.**

*Key words* Adjunctive therapy, Apraclonidine, Diurnal curve, Exfoliation glaucoma, Exfoliation syndrome, Intraocular pressure, Primary open-angle glaucoma, Pseudoexfoliation

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Exfoliation syndrome, an age-related condition which is common worldwide, is a major risk factor for the development of a severe glaucoma (exfoliation glaucoma) which leads to blindness in a significant proportion of affected patients.[1] Exfoliation glaucoma patients generally present with higher intraocular pressures (IOPs) and their IOP is more difficult to control than that in primary open-angle glaucoma patients.[2–9] Apart from the higher mean IOPs in exfoliation glaucoma, it has been shown recently that the range and peak IOPs throughout the day are greater than in primary open-angle glaucoma.[10] In addition, higher mean, range and peak IOPs continue to differentiate exfoliation and primary open-angle glaucoma despite treatment with monotherapy using timolol maleate.[11]

Because of the difficulty in controlling the IOP with a single agent in exfoliation glaucoma, it becomes important carefully to evaluate medicines that might be used as adjunctive therapy. Medicines that might be particularly effective in exfoliation glaucoma and minimise the IOP differences compared with primary open-angle glaucoma potentially could be of great benefit in preventing glaucomatous visual loss in patients who suffer from exfoliation glaucoma.

In this study we investigated the additive effect of apraclonidine 0.5% used three times daily in conjunction with timolol maleate 0.5%



 

solution used twice daily in exfoliation versus primary open-angle glaucoma patients.

## Materials and methods

We entered into this prospective study consecutive newly diagnosed phakic Greek patients with either exfoliation or primary open-angle glaucoma in whom therapy with timolol maleate 0.5% twice daily alone was deemed inadequate for controlling their IOP and whose IOP on this medicine was > 21 mmHg at 08:00 hours at the first diurnal curve. In patients with bilateral glaucoma one eye was randomly selected to be included in the study. Patients were diagnosed and followed at the Glaucoma Unit of the University Department of Ophthalmology, AHEPA Hospital, Thessaloniki, Greece which meets the ophthalmic needs of an urban and rural population of approximately 1.5 million people. All new eligible glaucoma patients who presented between July 1996 and June 1997 and were treated with timolol maleate 0.5% b.i.d. were invited to participate in this study. Some patients had been included in a previous report that detailed the effect of timolol on the diurnal curve of IOP.[11] Three patients declined participation due to the inconvenience of hospitalisation. All patients provided their written informed consent before participation in this study. A specially designed adverse experience report was completed for each patient receiving apraclonidine 0.5%.

The inclusion and exclusion criteria for this study were similar to those described previously.[2,10] Patients with conditions that might affect the accuracy and reliability of the IOP readings (e.g. concurrent ocular inflammation, previous ocular surgery, ophthalmic drugs, thyroid ophthalmopathy) were excluded. To facilitate age matching all primary open-angle glaucoma patients younger than 50 years and all exfoliation glaucoma patients older than 80 years were excluded from the study. Eligible patients by the above criteria were matched individually for age (± 2 years) between the exfoliation and primary open-angle glaucoma groups.[2,10] Upon admittance to the study a standard protocol was used in all patients.[10] An initial ocular examination was performed including Snellen visual acuity, Goldmann applanation tonometry, examination of the ocular adnexa, slit-lamp biomicroscopy, gonioscopy and stereoscopic visualisation of the fundus with the Volk 90 D lens. The Octopus 500 EZ perimeter (G1 program; analysis by Peridata 6.2c) was used for testing visual field defects. All glaucoma patients were comprehensively examined on presentation by slit-lamp biomicroscopy and gonioscopy to determine whether they had exfoliation or primary open-angle glaucoma. Patients included in the exfoliation glaucoma group had clinical evidence of exfoliation material in the anterior segment. By contrast, patients diagnosed as suffering from primary open-angle glaucoma had no evidence of exfoliation material. Information recorded on all patients included: sex, age, systemic disorders, systemic drugs and details of glaucoma at the time of diagnosis (IOP, cup-to-disc ratio, visual field). The mean defect, as determined by the Octopus perimeter, was used to assess the visual field.

Following the initial examination all patients were treated with timolol maleate 0.5% solution (Merck Sharp & Dohme/Vianex, Athens) twice daily with the dosing regimen set at 08:00 and 20:00 hours. Patients were admitted to hospital for the baseline 24 h diurnal curve of their IOP on timolol after at least 3 months of chronic dosing with timolol maleate. Pressure measurements were performed by the same investigators (D.A.M., T.M.) using the same instrument (Goldmann applanation tonometer). Patients were admitted in the morning and measurements were performed every 4 h at 10:00, 14:00, 18:00, 22:00, 02:00, 06:00 and 08:00 hours. At the 22:00 hours measurement patients were awake at bed rest. The 06:00 hours IOP measurement was performed immediately after waking. Patients were encouraged to carry on as normal a life as possible within the hospital.

Following discharge from the hospital all patients whose IOP was not controlled sufficiently by timolol alone (i.e. IOP > 21 mmHg at 08:00 hours) were started on apraclonidine 0.5% drops (Alcon Hellas, Athens) t.i.d. (dosing regimen set at 08:00, 14:00 and 20:00 hours). Patients were advised how to instil their eyedrops and were instructed for compliance with their medication. Apraclonidine drops were instilled approximately 10 min after timolol drops. Patients who could not comply were excluded. All 60 patients who completed the dosing regimen were readmitted approximately 2 months after their first diurnal IOP curve with timolol for a second 24 h IOP curve while using their apraclonidine and timolol drops.

Statistical analysis of the IOP at each time point was by an unpaired *t*-test between groups. A paired *t*-test was used to evaluate the reduction in IOP from baseline within groups after the addition of apraclonidine. Controlled IOP was defined as IOP of 21 mmHg or less at all six diurnal time points. An *F*-test was used to evaluate differences in standard deviations between groups at each time point.[12] The significance level was set at 5% and all tests were a two-way analysis.

## Results

### *Patients*

Table 1 summarises the 60 patients (30 patients in each group) who completed this study. No statistically significant differences were observed between the

**Table 1.** *Patient baseline data*

| | EXG group | POAG group | *p* value |
|---|---|---|---|
| Age (years) | 66.3 ± 6.5 | 68.3 ± 6.4 | 0.24 |
| Gender | | | |
| Male | 18 | 18 | 0.13 |
| Female | 12 | 12 | |
| Visual acuity | 0.7 ± 0.3 | 0.7 ± 0.4 | 0.49 |
| Cup/disc ratio | 0.7 ± 0.2 | 0.6 ± 0.3 | 0.37 |
| Visual field mean defect | 10.5 ± 5.7 | 8.2 ± 6.0 | 0.086 |

EXG, exfoliation glaucoma; POAG, primary open-angle glaucoma.

**Table 2.** *Baseline mean intraocular pressure (mmHg ± SD) on timolol maleate 0.5% solution*

| | EXG group | POAG group | *p* value of mean | *p* value of SD |
|---|---|---|---|---|
| 06:00 hours | 27.2 ± 8.2 | 23.8 ± 3.3 | 0.044 | < 0.001 |
| 10:00 hours | 27.9 ± 9.1 | 23.6 ± 4.4 | 0.022 | < 0.001 |
| 14:00 hours | 24.9 ± 8.2 | 22.8 ± 3.9 | 0.22 | < 0.001 |
| 18:00 hours | 24.0 ± 7.8 | 23.1 ± 4.1 | 0.55 | 0.001 |
| 22:00 hours | 23.2 ± 7.7 | 22.1 ± 3.6 | 0.47 | < 0.001 |
| 02:00 hours | 23.6 ± 7.6 | 22.2 ± 3.5 | 0.35 | < 0.001 |
| Maximum | 30.0 ± 8.9 | 25.8 ± 3.3 | 0.019 | < 0.001 |
| Minimum | 21.2 ± 7.0 | 20.2 ± 3.4 | 0.48 | < 0.001 |
| Range | 8.8 ± 3.6 | 5.5 ± 2.2 | > 0.001 | 0.01 |
| Diurnal | 25.1 ± 8.2 | 22.9 ± 3.8 | 0.19 | < 0.001 |

EXG, exfoliation glaucoma; POAG, primary open-angle glaucoma.

exfoliation and primary open-angle glaucoma patients for any baseline parameter ($p > 0.05$). Two patients did not complete the initial phasing protocol due to poor compliance and two others discontinued their participation because of an adverse event while taking apraclonidine.

### *Intraocular pressure*

A difference in baseline IOP values was observed at several time points (at 06:00 and 10:00 hours). Table 2 shows the baseline IOPs of the exfoliation and primary open-angle glaucoma patients prescribed timolol maleate only. There was also a higher mean maximum as well as mean range of IOP in the exfoliation glaucoma group than in the primary open-angle glaucoma group. Additionally, the standard deviation of IOPs among individuals was greater in the exfoliation than the primary open-angle glaucoma group at each time point ($p < 0.05$). The mean diurnal IOP on timolol maleate alone was 25.1 ± 8.1 mmHg in the exfoliation glaucoma group and 22.9 ± 3.8 mmHg in the primary open-angle glaucoma group ($p = 0.19$).

Following treatment with apraclonidine there was no statistically significant difference at any time point in the mean IOP between the exfoliation and primary open-angle glaucoma patients, although there was a trend to a slightly higher IOP in the exfoliation glaucoma group at most time points (Table 3). Forty-three per cent of exfoliation glaucoma patients and 27% of primary open-angle glaucoma patients had controlled IOPs on apraclonidine. In addition, no statistically significant difference was observed in the mean maximum or the mean range of IOP between groups ($p > 0.05$). However, the standard deviation of pressures at each time point continued to be higher in the exfoliation compared with the primary open-angle glaucoma group ($p < 0.05$). The mean diurnal IOP in the exfoliation glaucoma group was 20.5 ± 7.0 mmHg and in the primary open-angle glaucoma group, 20.0 ± 3.4 mmHg ($p = 0.73$).

Regarding the extent of the decrease in IOP (Table 4), both the absolute decrease and the percentage reduction were greater in the exfoliation compared with the primary open-angle glaucoma group at most time points ($p < 0.05$). The exception to this was the early morning (02:00 hours) pressure measurement, when the exfoliation and primary open-angle glaucoma groups had little difference between groups or a reduction from baseline within each group.

### *Safety*

Three of 60 patients (5%) who completed the dosing regimen developed ocular intolerance to apraclonidine over the 2 months of therapy. These patients tolerated the medication sufficiently to complete the diurnal curve successfully. Two additional patients developed ocular intolerance but were dropped from the study prior to their second diurnal curve, providing an overall incidence of 8% (5 of 62 patients).

Regarding ocular and systemic symptoms, 6 patients (10%) reported other side effects potentially related to the use of apraclonidine. Of these, 4 experienced ocular side effects (burning and stinging after administration in 2

**Table 3.** *Mean intraocular pressure (mmHg ± SD) on apraclonidine 0.5% and timolol maleate 0.5%*

| | EXG group | POAG group | *p* value of mean | *p* value of SD |
|---|---|---|---|---|
| 06:00 hours | 21.3 ± 7.4 | 20.2 ± 4.2 | 0.37 | < 0.001 |
| 10:00 hours | 21.2 ± 7.8 | 20.1 ± 3.3 | 0.47 | < 0.001 |
| 14:00 hours | 20.0 ± 6.7 | 19.3 ± 3.3 | 0.49 | < 0.001 |
| 18:00 hours | 19.1 ± 6.2 | 19.7 ± 3.2 | 0.61 | < 0.001 |
| 22:00 hours | 19.6 ± 7.5 | 20.3 ± 3.1 | 0.62 | < 0.001 |
| 2:00 hours | 21.7 ± 6.5 | 20.1 ± 3.5 | 0.62 | < 0.001 |
| Maximum | 24.2 ± 8.7 | 22.6 ± 3.2 | 0.25 | < 0.001 |
| Minimum | 17.6 ± 5.1 | 17.7 ± 3.0 | 0.36 | 0.01 |
| Range | 6.6 ± 4.5 | 4.9 ± 2.5 | 0.98 | < 0.001 |
| Diurnal | 20.5 ± 7.0 | 20.0 ± 3.4 | 0.73 | < 0.001 |

EXG, exfoliation glaucoma; POAG, primary open-angle glaucoma.

**Table 4.** *Percentage and absolute intraocular pressure (mmHg ± SD) reduction from baseline*

| Time | Percentage reduction | | | Absolute reduction | | |
|---|---|---|---|---|---|---|
| | EXG group | POAG group | *p* value | EXG group | POAG group | *p* value |
| 06:00 hours | 21.2% ± 12% | 15.3% ± 13% | 0.081 | 5.8 ± 3.9 | 3.6 ± 2.8 | 0.017 |
| 10:00 hours | 23.2% ± 14% | 13.7% ± 12% | 0.0093 | 6.8 ± 5.3 | 3.5 ± 2.9 | 0.0079 |
| 14:00 hours | 17.4% ± 17% | 14.1% ± 15% | 0.43 | 4.8 ± 5.4 | 3.5 ± 3.5 | 0.26 |
| 18:00 hours | 19.4% ± 14% | 13.4% ± 13% | 0.096 | 4.9 ± 4.3 | 3.3 ± 3.2 | 0.12 |
| 22:00 hours | 14.9% ± 16% | 6.77% ± 14% | 0.047 | 3.6 ± 3.8 | 1.8 ± 2.9 | 0.044 |
| 02:00 hours | 6.70% ± 15% | 9.07% ± 11% | 0.49 | 2.0 ± 3.6 | 2.1 ± 2.8 | 0.88 |
| Maximum | 32.3% ± 11% | 25.3% ± 9% | 0.012 | 9.4 ± 5.0 | 6.1 ± 2.2 | 0.0049 |
| Minimum | 0.035% ± 14% | −2.58% ± 13% | 0.47 | 0.4 ± 3.2 | −0.3 ± 2.5 | 0.38 |

EXG, exfoliation glaucoma; POAG, primary open-angle glaucoma.

patients; pruritus and 'dry eye' sensation in 2 patients) while 2 patients reported related, non-ocular side effects (weakness, dizziness and headache). These side effects did not affect the investigation but resulted in discontinuation of the medication after completion of the diurnal curve.

After completing the study, depending on the outcome of a patient's diurnal curve with apraclonidine and timolol and the existence of side effects, the appropriate management steps were taken and all patients were followed routinely to determine the long-term stability of the visual field and optic disc.

## Discussion

Apraclonidine is both an $\alpha_1$- and $\alpha_2$-adrenergic agonist with relative selectivity for $\alpha_2$-receptors.[13] Gharagozloo and associates[14] have shown that apraclonidine reduces the IOP primarily as an aqueous suppressant.

In patients with primary open-angle glaucoma or ocular hypertension apraclonidine has been studied as either monotherapy or adjunctive therapy. As monotherapy, Stewart and associates[15] in a multicentre study showed that both 0.25% and 0.5% apraclonidine given three times daily have an ocular hypertensive efficacy equal to that of timolol maleate 0.5% at 8 h after administration. However, at the 12 h trough level both concentrations of apraclonidine caused approximately a 15% reduction in IOP, which was statistically less than that caused by timolol maleate. These effects were observed for 3 months.[15] As adjunctive therapy, in a multicentre study Stewart and associates[16] showed that both 0.5% and 1.0% apraclonidine given twice a day provided a 14% additional reduction in IOP over timolol maleate alone for up to 3 months.

Apraclonidine added to maximally tolerated medical therapy has been evaluated in a multicentre study by Robin and associates,[17] who found an additional 11% reduction in IOP in these patients. Sixty per cent of patients had their glaucoma controlled without surgical therapy for as long as 5 months versus 32% of those who received placebo.[17] By far the most common anterior segment side effect of apraclonidine is anterior segment intolerance, which has been reported in 8–36% of patients.[18]

In the current study we investigated the effect on the IOP control and safety of adding apraclonidine 0.5% three times daily to the medication of patients with exfoliation or primary open-angle glaucoma whose IOP was inadequately controlled on timolol maleate solution 0.5% alone dosed twice daily. This study found that adding apraclonidine to timolol maleate caused a significant reduction in IOP in both the exfoliation and primary open-angle glaucoma groups throughout the 24 h time period. However, the percentage reduction as well as the absolute decrease in IOP was greater in exfoliation glaucoma than in primary open-angle glaucoma patients. Following treatment with apraclonidine the mean IOPs at each time point, as well as the peak and range of pressures observed throughout the day, became statistically similar to those in primary open-angle glaucoma, although the standard deviation of pressures remained higher in the exfoliation group. Consequently, the addition of apraclonidine to timolol maleate produced IOP characteristics that were more similar between primary open-angle glaucoma and exfoliation glaucoma patients. This is a change from previous studies, in which exfoliation patients had higher IOPs on no therapy or on monotherapy with timolol maleate.[10,11] In addition, the efficacy of apraclonidine is maintained for at least 2 months after beginning therapy.

The percentage reduction of IOP with apraclonidine was greater in the exfoliation group in half of the measured time points compared with the primary open-angle glaucoma patients. The reasons for this effect are not entirely clear. The hypothesised mechanism for the development of exfoliation glaucoma has been blockage of the trabecular meshwork by exfoliation material, pigment and both of these together.[19–21] The density of pigment on the trabecular meshwork has been correlated with the presence and severity of glaucoma. Consequently, reduced aqueous production in our study might have had a greater effect in exfoliation glaucoma than in primary open-angle glaucoma. However, data on the influence of these mechanisms in determining the treatment response to the various antiglaucoma medications are lacking. It is conceivable that a number of anatomical and physiological factors influence the response of exfoliation glaucoma patients to a given medication.

A greater ocular hypotensive effect in exfoliation glaucoma compared with primary open-angle glaucoma has been shown previously with timolol maleate as

monotherapy.[11] However, timolol monotherapy did not produce similar IOP levels between groups. Perhaps, however, adjunctive therapy may generally be required to achieve this goal. Whether the pharmacological profile of apraclonidine allows for a greater response in exfoliation glaucoma compared with other glaucoma medicines that might be used adjunctively remains unknown.

Safety between groups appeared similar between medicines, with the expected incidence of anterior segment intolerance for 2 months of therapy and the low rate of systemic side effects.[22]

In the future it will be important to document whether other medicines commonly used as early adjunctive therapy for glaucoma, such as dorzolomide, brimonidine or latanoprost, could also equalise the IOPs between exfoliation and primary open-angle glaucoma patients when these drugs are added to timolol maleate. Further clinical work is required to determine the optimal treatment regimens and risk factors for progression for patients with exfoliation glaucoma.

This study suggests that apraclonidine, when combined with timolol maleate, is associated with generally similar IOP control in exfoliation glaucoma patients and primary open-angle glaucoma patients.

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