Twenty-four hour intraocular pressure reduction with latanoprost compared with pilocarpine as third-line therapy in exfoliation glaucoma

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CLINICAL STUDY

Abstract

Purpose **To compare the 24 hour efficacy of latanoprost 0.005% given every evening with that of pilocarpine 4% given four times daily as third-line therapy in patients with exfoliation glaucoma receiving timolol 0.5% and dorzolamide 2% each given twice daily.**
Method **We enrolled 30 patients with exfoliation glaucoma not adequately controlled on timolol maleate 0.5% and dorzolamide 2%. Each patient underwent a baseline 24 hour intraocular pressure curve testing at 06:00, 10:00, 14:00, 18:00, 22:00 and 02:00 hours. Patients were randomised to receive either latanoprost 0.005% or pilocarpine 4% for a minimum of 8 weeks and were then crossed over to the opposite therapy. Diurnal curve testing was repeated at the end of each treatment.**
Results **There was a significant decrease from baseline in intraocular pressure at each timepoint for both study medicines ($p < 0.016$). Latanoprost provided better intraocular pressure control than pilocarpine at daytime measuresments (17.4 vs 19.7 mmHg at 06:00 hours, $p < 0.001$; 17.8 vs 19.1 mmHg at 10:00 hours, $p = 0.04$). However, pilocarpine reduced the pressure more than latanoprost at 22:00 hours (18.4 vs 19.5 mmHg, $p = 0.016$). Overall, the diurnal intraocular pressure was reduced from a baseline of 21.5 ± 3.7 mmHg to 18.8 ± 3.1 mmHg on pilocarpine and to 18.0 ± 3.0 mmHg on latanoprost ($p = 0.06$). In addition, mean peak pressure was similar between pilocarpine (21.0 ± 2.9 mmHg) and latanoprost (20.5 ± 3.8 mmHg) ($p = 0.20$). Side-effects were similar with the exception of blurred vision, which was only found with pilocarpine (10%). Compliance was more difficult with pilocarpine.**
Conclusion **In exfoliation glaucoma, as a third-line adjunctive therapy added to timolol and dorzolamide, latanoprost and pilocarpine have similar diurnal efficacy. However, latanoprost provides a greater morning pressure reduction.**

Key words Dorzolamide, Exfoliation glaucoma, IOP, Latanoprost, Timolol

Exfoliation glaucoma is generally considered a severe form of hypertensive chronic open angle glaucoma.[1] Recent information has indicated that presenting intraocular pressures in exfoliation glaucoma are higher and more difficult to control than those in primary open angle glaucoma.[2,3] Furthermore, glaucomatous damage occurs more rapidly in exfoliation glaucoma compared with primary open angle glaucoma.[4] Consequently, determining effective medical stepwise therapy in exfoliation glaucoma is especially important to help control these patients.

Unfortunately, to date there are few comparative studies with respect to the efficacy of medications in controlling the intraocular pressure in exfoliation glaucoma. Recently, Konstas and co-workers[5] showed that as primary therapy timolol maleate solution twice daily controlled exfoliation glaucoma patients similarly to timolol maleate gel once daily. Also, Konstas and associates demonstrated in separate studies in exfoliation glaucoma patients that when added to timolol, apraclonidine further reduced the pressure by 17% and dorzolamide by 18%.[6,7]

In the current study we evaluated the 24 hour efficacy and safety of pilocarpine 4% given four times daily versus latanoprost 0.005% once daily added to dorzolamide 2% and timolol maleate solution 0.5%, both given twice daily, in exfoliation glaucoma.

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Patients and methods

Patients selected for this prospective study attended the glaucoma clinic of the University Department of Ophthalmology, AHEPA Hospital, Thessaloniki, Greece between June 1997 and June 1998. We included in this investigation all exfoliation glaucoma patients of either sex who were: (i) older than 50 years of age, (ii) required a lower intraocular pressure to prevent glaucomatous progression despite combination therapy of timolol and dorzolamide and (iii) demonstrated on these medicines an intraocular pressure ⩾20 mmHg at at least one timepoint during the baseline 24 hour period. Moreover, patients must have demonstrated a typical glaucomatous visual field loss (nasal step, or arcuate, paracentral or Seidel's scotoma) as determined by automated static threshold perimetry (Octopus 500 EZ, G1 programme, Zurich) and glaucomatous optic nerve head cupping (neural rim notching or saucerisation).

Patients were excluded from this study if they demonstrated a history of ocular surgery/trauma, previous use of steroids, contact lens use, dry eyes, corneal abnormality, or any condition that prevented reliable applanation tonometry. Also excluded were patients with: evidence of ocular infection, inflammation or history of renal or hepatic impairment or moderate to severe cataract. In patients with bilateral exfoliation glaucoma one eye was randomly selected to be included in this study.

Thirty-five consecutive Greek patients with exfoliation glaucoma were enrolled of whom 30 completed the study. Of the patients who failed to complete, 1 discontinued due to the inconvenience of hospitalisation, 1 patient could not obtain latanoprost drops from his medical insurance doctor; and 3 patients withdrew due to ocular allergy to either pilocarpine or latanoprost drops. Of the 30 patients included in this study, 22 had undergone the baseline 24 hour curve (timolol and dorzolamide treated curve) previously as part of another study.[7]

The methods for the present study were similar to those described previously.[2,3] All 30 patients who completed the present study underwent 24 hour measurements of their intraocular pressure on three separate occasions. The first baseline diurnal curve of exfoliation glaucoma patients was performed with timolol and dorzolamide both given twice daily. Patients were then randomly assigned to either pilocarpine 4% (Alcon Hellas, Athens) or latanoprost 0.005% (Pharmacia & Upjohn (Hellas) Athens). The two subsequent diurnal curves were performed after a minimum of 2 months treatment with pilocarpine 4% at 07:45, 14:00, 20:30 hours and bedtime, or latanoprost 0.005% at 20:30 hours. The period of 2 months was chosen to avoid a carry-over effect of the medications under investigation. During the assessment of the baseline 24 hour curve all exfoliation glaucoma patients were treated with timolol maleate 0.5% and dorzolamide 2% solutions (Merck Sharp & Dohme/Vianex, Athens) twice daily with the dosing regiment set at 08:00 and 20:00 hours for timolol and approximately 15 min later for dorzolamide. Subsequently all exfoliation glaucoma patients were randomised in a crossover fashion to treatment with latanoprost 0.005% or pilocarpine 4%.

Diurnal curves for intraocular pressure were obtained by the same investigator (A.M.) using the same calibrated instrument (Goldmann applanation tonometer). Patients were admitted in the morning and measurements were recorded at 10:00, 14:00, 18:00, 22:00, 02:00 and 06:00 hours. At the 22:00 hour measurement patients were awake at bed rest. The 06:00 hour intraocular pressure measurement was performed immediately after wakening. Patients were encouraged to lead as normal a life as possible within the confines of the hospital.

Patients were instructed regarding medication instillation and compliance. At each visit local and systemic side-effects that occurred during the treatment period were recorded. Follow-up visits and appropriate treatment steps were scheduled according to the results of the diurnal curves.

Statistics

Statistical analyses for intraocular pressure for intra- and inter-group analyses were performed using a paired *t*-test.[8] An *F*-test was used to evaluate differences in the standard deviations between the different treatments at each timepoint.[8] The significance level was set at 5% and a two-way analysis was used for all tests. This study had an 80% power to exclude a 1.0 mmHg difference assuming a standard deviation of 1.8 mmHg between treatment periods.[9,10] Adverse events were evaluated by a McNemar test.[11]

Results

Patients

Seventeen men and 13 women (30 patients) with exfoliation glaucoma completed this study who had a mean age of 68.1 years (range 54–76 years). All patients were white. The mean baseline parameters of these 30 patients were mean visual acuity 0.7 (SD ± 0.3), mean vertical cup-to-disc ratio 0.7 (SD ± 0.1) and mean deviation of 13.3 dB (SD ± 5.8) on visual field testing.

Intraocular pressure

The baseline intraocular pressures (treated values with timolol and dorzolamide twice daily) and treatment period pressures are shown in Table 1. Differences from baseline and between treatments are shown in Table 2. Compared with baseline measurements both latanoprost and pilocarpine caused a significant reduction in intraocular pressure at each timepoint throughout the 24 hour period.

Latanoprost caused a greater reduction than pilocarpine from baseline at the 06:00 and 10:00 timepoints. However, pilocarpine caused a lower pressure at 22:00 hours and demonstrated a diurnal

Table 1. *Baseline 24 hour intraocular pressure values (patients treated with timolol and dorzolamide), treatment period pressures and statistical comparisons between baseline and treatment values*

Time (hours)	Baseline	Latanoprost	Pilocarpine	Baseline vs latanoprost	Baseline vs pilocarpine	Latanoprost vs pilocarpine
06:00	21.93 ± 4.21	17.43 ± 3.42	19.77 ± 3.20	$p<0.001$	$p<0.001$	$p<0.001$
10:00	23.27 ± 4.29	17.83 ± 3.25	19.10 ± 3.00	$p<0.001$	$p<0.001$	$p=0.042$
14:00	21.17 ± 3.83	17.87 ± 3.20	18.33 ± 3.28	$p<0.001$	$p<0.001$	$p=0.347$
18:00	21.17 ± 4.06	17.67 ± 3.25	18.13 ± 3.49	$p<0.001$	$p<0.001$	$p=0.400$
22:00	20.63 ± 4.25	19.50 ± 4.26	18.40 ± 3.76	$p<0.016$	$p<0.001$	$p=0.016$
02:00	21.00 ± 4.12	19.00 ± 4.05	18.93 ± 4.17	$p<0.001$	$p<0.001$	$p=0.900$
Diurnal	21.53 ± 3.74	18.00 ± 3.04	18.78 ± 3.14	$p<0.001$	$p<0.001$	$p=0.204$
Max.	24.53 ± 4.03	20.47 ± 3.80	21.00 ± 3.59	$p<0.001$	$p<0.001$	$p=0.327$
Min.	19.10 ± 3.45	16.13 ± 3.13	16.53 ± 2.94	$p<0.001$	$p<0.001$	$p=0.060$
Range	5.37 ± 1.71	4.33 ± 1.99	4.50 ± 1.70			

pressure statistically similar to latanoprost. In addition, the average peak intraocular pressure was similar between groups.

Regarding the distribution of intraocular pressure as indicated by the standard deviation, no differences between pilocarpine and latanoprost were noted at any timepoint or the diurnal average. Although patients complied for the duration of the study the majority found compliance far more difficult with pilocarpine.

Adverse events

Of the 5 patients who discontinued the study early, 3 (9%) did so due to an adverse event (ocular allergy). Two (6%) of these were during pilocarpine treatment and one (3%) during latanoprost treatment.

Of the 30 patients completing the study, 3 (10%) complained of blurred vision with pilocarpine. This side-effect was not observed with latanoprost. One patient experienced browache and headache with pilocarpine (3%). One patient (3%) complained of dizziness with latanoprost. These side-effects did not affect the investigation but resulted in discontinuation of the medications after the end of the study period. In addition, 5 patients (17%) in the latanoprost arm and 4 (13%) in the pilocarpine arm experienced stinging and 'dry eye sensation' thought to be associated with punctate epitheliopathy. Finally, 2 patients (7%) on pilocarpine and one patient (3%) on latanoprost experienced chronic moderate conjunctival redness. No difference existed between groups for any individual side-effect or the overall number of patients who experienced an adverse event ($p > 0.05$).

Table 2. *Reduction in intraocular pressure from baseline in patients with exfoliation glaucoma receiving latanoprost or pilocarpine as third-line therapy*

	Latanoprost		Pilocarpine	
Time (hours)	Reduction from baseline	% reduction	Reduction from baseline	% reduction
06:00	4.50 ± 2.67	20.52	2.17 ± 2.38	9.90
10:00	5.43 ± 3.04	23.33	4.17 ± 2.26	17.92
14:00	3.23 ± 2.28	15.26	2.83 ± 2.20	13.37
18:00	3.50 ± 2.18	16.53	3.03 ± 2.72	14.31
22:00	1.13 ± 2.43	5.48	2.23 ± 1.91	10.81
02:00	2.00 ± 2.65	9.52	2.00 ± 1.91	9.52
Max.	4.30 ± 2.15	17.53	3.47 ± 2.01	14.14
Min.	2.97 ± 2.54	15.55	2.77 ± 1.83	14.50
Diurnal	3.56 ± 2.04	16.54	2.75 ± 1.57	12.77

Discussion

Latanoprost, an $F_{2\alpha}$ prostaglandin, is highly selective for the FP receptor and reduces intraocular pressure by increasing uveoscleral outflow.[12] In ocular hypertensive and primary open angle glaucoma patients, latanoprost reduced the intraocular pressure by between 25% and 36% for as long as 2 years.[13–15] When compared with timolol maleate 0.5% twice daily, latanoprost 0.005% once daily has demonstrated either an equal or statistically greater reduction in intraocular pressure in American and Scandinavian multicentre studies,[13,14] but not the UK multicenter study.[15] In contrast, pilocarpine directly stimulates cholinergic receptors which lowers the intraocular pressure by increasing the conventional outflow facility.[16] Although diurnal efficacy is poorly studied, one report[17] found an average decrease in intraocular pressure of about 20%.

In the present study we evaluated the efficacy and safety of pilocarpine 4% given four times daily compared with latanoprost 0.005% given every evening as third-line therapy to dorzolamide 2% and timolol maleate 0.5% solution both given twice daily. This study showed that both pilocarpine and latanoprost caused a significant reduction in intraocular pressure from baseline (dorzolamide and timolol therapy) at each measured timepoint over 24 hours. When treatment periods were compared, the mean diurnal pressures (mean of six measurements over a 24 hour period) on latanoprost and pilocarpine were statistically equal, although there was a trend towards greater diurnal efficacy of latanoprost. In addition, the mean peak intraocular pressure for each patient was equal between groups. Latanoprost, however, was more effective statistically in reducing the intraocular pressure than pilocarpine in the morning hours (6:00, 10:00 hours). In contrast, pilocarpine was more effective at 22:00 hours than latanoprost.

The fact that latanoprost did not statistically lower the diurnal intraocular pressure more than pilocarpine in our study was a surprise to the authors. The reasons for

the similar efficacy could not be completely explained but may include the fact that since the exfoliation glaucoma patients were already being treated with two aqueous suppressants (timolol and dorzolamide) the ability of a third drug to reduce the intraocular pressure sufficiently to demonstrate a statistical difference between treatments is diminished, despite latanoprost supposedly having a greater potential efficacy. However, to our knowledge, no comparative trials of latanoprost and pilocarpine as monotherapy have been performed to determine any difference in efficacy.

Second, pilocarpine may be more efficacious in exfoliation glaucoma compared with primary open angle glaucoma. It is well established that physiological pupillary movements and especially pharmacological mydriasis may increase intraocular pressure considerably in exfoliation glaucoma.[1] By constricting the pupil and eliminating movement of the iris pigment epithelium over the roughened lens surface (from exfoliative protein) pilocarpine could have reduced pigment dispersion providing a further lowering in intraocular pressure. However, the precise effect of pilocarpine in diminishing pigment liberation and intraocular pressure requires further elucidation with a long-term controlled study.

Of interest also was the lower mean intraocular pressure on latanoprost in the morning compared with pilocarpine. The importance of this remains unclear in that it still is unknown whether a reduced pressure at any specific time in a 24 hour period is important in preventing progression. The reduced daytime pressures with latanoprost, however, are consistent with previous monotherapy diurnal data regarding latanoprost dosed at night,[18] which showed that peak pressures were lowest between 12 and 24 hours after dosing. In our study night-time pressures with latanoprost were approximately 1.3–2.0 mmHg higher than daytime values, which helped to produce the statistically equal diurnal curve relative to pilocarpine.

This study showed that in exfoliation glaucoma, latanoprost and pilocarpine as a third-line adjunctive therapy added to timolol and dorzolamide have similar diurnal efficacy and safety. However, latanoprost provides a greater morning pressure reduction. This study did not evaluate these two medicines in patients with primary open angle glaucoma, for which the results potentially could have differed. The present study evaluates the initial response to the medications and thus can not address the subject of tachyphylaxis. Further study is needed regarding the efficacy and safety of newer medications as late adjunctive therapy to determine the most appropriate stepwise therapy in exfoliation glaucoma patients.

References

1. Ritch R. Exfoliation syndrome and occludable angles. Trans Am Ophthalmol Soc 1994;92:845–944.
2. Konstas AGP, Mantziris DA, Stewart WC. Diurnal intraocular pressure in untreated exfoliation and primary open-angle glaucoma. Arch Ophthalmol 1997;115:182–5.
3. Konstas AGP, Mantziris DA, Cate EA, Stewart WC. Effect of timolol on the diurnal intraocular pressure in exfoliation and primary open-angle glaucoma. Arch Ophthalmol 1997;115:975–9.
4. Pohjanpelto P. Long-term prognosis of visual field in glaucoma simplex and glaucoma capsular. Acta Ophthalmol 1985;63:418–23.
5. Konstas AGP, Mantziris DA, Maltezos A, Cate EA, Stewart WC. Comparison of the 24 hour control with Timoptic 0.5% and Timoptic-XE 0.5% in exfoliation and primary open-angle glaucoma. Acta Ophthalmol Scand 1999;77:541–3.
6. Konstas AGP, Maltezos A, Mantziris DA, Sine CS, Stewart WC. The comparative ocular hypotensive effect of apraclonidine with timolol maleate in exfoliation versus primary open-angle glaucoma patients. Eye 1999;13:314–8.
7. Konstas AGP, Maltezos A, Bufidis T, Hudgins AC, Stewart WC. Twenty-four hour control of IOP with dorzolamide and timolol maleate in exfoliation and primary open-angle glaucoma. Eye 2000;14:73–7.
8. Book SA. Essentials of statistics. New York: McGraw Hill, 1978:117–22, 205–15.
9. Mundorf TK, Cate EA, Sine CS, Otero DW, Stewart JA, Stewart WC. The safety and efficacy of switching timolol maleate 0.5% solution to timolol hemihydrate 0.5% solution given twice daily. J Ocul Pharm Ther 1998;14:129–35.
10. Duff GR. A double-masked crossover study comparing the effects of carteolol 1% and 2% on intraocular pressure. Acta Ophthalmol 1987;65:618–21.
11. Siegel S. Nonparametric statistics. Series in psychology. New York: McGraw Hill, 1956:63–7.
12. Gabelt BT, Kaufman PL. Prostaglandin $F_{2\alpha}$ increases uveoscleral outflow in the cynomolgus monkey. Exp Eye Res 1989;49:389–402.
13. Alm A, Stjernschantz J, Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side-effects of 0.005% latanoprost applied once daily, evening or morning: a comparison with timolol. Ophthalmology 1995;102:1743–52.
14. Camras CB, the United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month, masked, multicenter trial in the United States. Ophthalmology 1996;103:138–47.
15. Watson PG, Stjernschantz J, the Latanoprost Study Group. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. Ophthalmology 1996;103:126–37.
16. Grierson I, Lee WR, Abraham S. Effects of pilocarpine on the morphology of the human outflow apparatus. Br J Ophthalmol 1978;62:302–13.
17. Harris LS, Galin MA. Dose response analysis of pilocarpine-induced ocular hypotension. Arch Ophthalmol 1970;84:605–8.
18. Konstas AGP, Maltezos AC, Gandi S, Hudgins AC, Stewart WC. Comparison of the 24 hour intraocular pressure reduction with two dosing regimes of latanoprost and timolol in patients with open-angle glaucoma. Am J Ophthalmol 1999;128:15–20.