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A randomized, comparative open-label study on the efficacy of latanoprost and timolol in steroid induced ocular hypertension after photorefractive keratectomy

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PURPOSE. *To evaluate the effect of 0.005% latanoprost and 0.50% timolol for the treatment of steroid-induced ocular hypertension (SIOH) after excimer laser photorefractive keratectomy (PRK).*

METHODS. *In this comparative, open-label study we enrolled 29 patients who received steroid therapy after PRK and developed intraocular pressure (IOP) elevation within 30 days of treatment. Fifteen were randomized to 0.005% latanoprost (group A) and 14 to 0.50% timolol (group B). IOP measurements were scheduled at 1, 3, 7, 15, 30, 60, 90 and 120 days of therapy.*

RESULTS. *We did not find any real differences between latanoprost and timolol except at the 7-day and 15-day timepoints, when latanoprost reduced IOP significantly more than timolol (p=0.033, 0.035, respectively). After 7 days of therapy two of the 14 timolol-treated patients had high IOP (24 and 26 mmHg) but these promptly returned to normal when latanoprost was added. No significant differences were observed in the ocular side effects considered.*

CONCLUSIONS. *0.005% latanoprost is as safe and effective as 0.50% timolol in the treatment of SIOH after PRK. Both drugs provide a significant and stable IOP reduction in the majority of patients after short-term treatment. These findings are encouraging for the use of latanoprost in the management of SIOH after PRK, although further trials are necessary to consider it as a primary treatment. (Eur J Ophthalmol 2000; 10: 205-11)*

KEY WORDS. *Latanoprost, Timolol, Steroid-induced ocular hypertension, PRK, Uveo-scleral outflow*

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INTRODUCTION

Steroid-induced ocular hypertension (SIOH) is defined as increased intraocular pressure (IOP) with reduced aqueous humour outflow after topical, periocular or oral glucocorticoids (1). The risk of ocular hypertension is higher in patients with a history of open angle glaucoma (2-7), diabetes mellitus (8), and severe myopia (9, 10).

According to Becker and Armaly (5, 11), topical glucocorticoids increase IOP after 4-6 weeks by up to 30 mmHg in 4-6% of otherwise healthy subjects, defined as “high responders”, whereas 30% of the normal population may be considered “intermediate responders”, with an IOP increase of at least 6 mmHg or attained IOP of 20 mmHg or higher. The IOP increase due to long-term steroid therapy may subside at the end of the treatment without any visual field defect or optic nerve damage, or it may cause optic nerve atrophy if ocular hypertension persists (12, 13).

Over the last few years, SIOH has gradually lost clinical relevance with the introduction of newer agents,

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which cause much smaller IOP rises than dexamethasone (e.g. fluorometholone, clobethasone), and with less traumatic surgical procedures (14-18). Therefore, ophthalmic surgeons have used glucocorticoids less, while the importance of non-steroid antiinflammatory drugs (NSAID) has increased (19-22).

However, since the introduction of excimer laser refractive surgery the probelm of SIOH has arisen once more. Photorefractive keratectomy (PRK) has become the safest and most popular refractive procedure, but SIOH occurs with high and unusual frequency. Several investigations showed an increased risk of ocular hypertension associated with topical steroid treatment after PRK, depending on differences between glucocorticoids (dexamethasone, clobethasone, fluorometholone), and ranging from 3 up to 30% (15, 17, 23-26). To date, the most common way to treat ocular hypertension after PRK is to suspend steroids and administer β-blockers (27). The purpose of this open-label study was to evaluate the efficacy of latanoprost in patients with high IOP as a result of steroid therapy after PRK.

MATERIALS AND METHODS

Between December 1997 and January 1999, 742 patients asked to undergo excimer laser surgery for myopia at the Department of Ophthalmology, University of Bari, Italy. After a short briefing, each patient gave informed consent. Detailed ocular and general medical history was collected. A complete ophthalmologic examination was done by the same physician (M.V.), which included slit-lamp biomicroscopy, uncorrected (UCVA) and best spectacle-corrected visual acuity (BCVA) reported on the logarithm of the minimum angle of resolution (LogMAR) scale (28), cycloplegic refraction using an autorefractometer, and altimetric corneal topography with pupillometry (Orbscan, Orbtek, Salt Lake City, Utah).

General exclusion criteria were: evidence of ocular disorders (infectious, inflammatory, degenerative) in the medical history (15 patients: 5 with a history of herpetic keratitis, 10 with keratoconus), untreated IOP higher than 21 mmHg (11 patients), wound healing abnormalities (e.g. keloids) (6 patients), intolerance to one of the components of the therapeutic eyedrops (5 patients), systemic diseases (diabetes mellitus type I: 4 patients, collagen vascular diseases: 3 patients), pregnancy (3 patients).

General inlcusion criteria were: age 18 to 55 years, stable refraction for at least two years, attempted myopic correction between –1.5 and –12 diopters (D) and regular astigmatism, as shown by corneal topography. We also excluded 55 patients with myopic refraction greater than 8 D, since postoperative IOP measurements could be affected by the reduction in corneal thickness (29).

A total of 640 patients met all the preoperative inclusion criteria and underwent PRK. Excimer laser surgery was performed by the same operator (M.V.) using a Laserscan 2000 (Lasersight, Orlando, FL). On completion of the surgical treatment, the ablated surface was moistened with a drop of netilmicin (Nettacin, SIFI, Catania, Italy) and 0.03% flurbiprofen sodium preservative-free ophthalmic solution (Ocufen, Allergan, Rome, Italy), then a soft contact lens was applied (Acuvue, Johnson and Johnson Prod. Inc., Jacksonville, FL). Topical flurbiprofen and a tetracycline-betamethasone-naphazoline combination (Alfaflor, Alfa Intes, Naples, Italy) were prescribed four times a day to all patients until re-epithelialization. Subjects were advised to take additional analgesic tablets (ketorolac tromethamine, Lixidol, 10 mg tablets, Farmitalia, Milano, Italy) if pain was not controlled properly by topical therapy.

After this first postoperative phase, all patients received a topical steroid, according to our therapeutic protocol: 0.1% fluorometholone acetate (Flarex, Alcon, Milano, Italy) was prescribed for attempted myopic corrections up to –6 D, and dexamethasone (Luxazone, Allergan, Roma, Italy) for attempted myopic correction over –6 D. Both drugs were applied four times a day for one month and thereafter the frequency was reduced every 20 days.

Postoperative examinations were done every 24 hours until re-epithelialization, then after 15 days and 1, 2, 3, and 4 months.

Twenty-nine patients (4.5%) had significantly high IOP between 15 and 30 days postoperatively. All these patients were enrolled in the study after informed consent was once more obtained. The cup/disc ratio was less than 0.4 in all subjects and no evidence of glaucoma was found in the family history.

Patients were randomly divided into two groups: 15 patients (15 eyes) were assigned to group A and 14

patients (14 eyes) to group B. The randomization code was computer-generated and assignments were made by the same physician (A.M.). The allocation code was broken only after completion of the statistical analysis. Group A patients applied 0.005% latanoprost eyedrops once daily (at 8 pm), and group B patients received 0.50% timolol twice daily (at 8 am and 8 pm). IOP was measured by the same physician (G.M.Q.) after 1, 3, 7 and 15 days of hypotensive treatment. Thereafter, tonometric evaluation was included in the follow-up schedule and was done monthly until 30 days after steroid withdrawal. In order to avoid bias, this observer (G.M.Q.) was not aware of the treatment assigned to each patient.

In case of failure of the hypotensive drug after seven days of treatment, adding the other drug to the therapeutic protocol was planned but as the resulting IOP values were not comparable, we excluded this data from the analysis.

Statistical methods: Minimum sample size was calculated to give the standard 80% chance of detecting a mean difference of 0.1 between groups assuming a value of 0.05 for alpha. Preoperative variables (age, sex, attempted myopic correction, basal IOP) and outcome (peak IOP, post-peak IOP) were recorded on a spreadsheet and analysed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA, version 5.0) and Winks Kwikstat (TexaSoft, Cedar Hill, TX, USA, version 4.5) as statistical analysis tools. Since all patients were examined at each timepoint we had no missing data. The continuous variables were compared by one-way within subjects ANOVA and paired Student's t-test, and categorical variables were analysed by a chi-square test. Differences were considered statistically significant for probabilities smaller than 0.05.

RESULTS

Table I shows the preoperative data. The groups did not differ with regard to age, sex, attempted correction and basal IOP. Among the 217 patients treated with dexamethasone, 15 (6.9%) had a significant IOP increase, as did 14 (3.3%) of the 423 given 0.1% fluorometholone acetate.

Stratifying all subjects according to the steroid administered after PRK, mean peak IOP was significantly lower (p=0.007) with fluorometholone than dexamethasone (mean peak IOP ± SD: 22.14 ± 2.77 and 27.47 ± 6.209 mmHg).

As shown in Table II, in group A mean IOP was significantly lower than group B after 7 and 15 days of hypotensive therapy (p = 0.033, p = 0.035, respectively). In group A, 8 patients (53.3%) achieved IOP less than 20 mm Hg within 24 hours and 13 (86.6%) achieved this after three days of treatment. All the patients had IOP less than 20 mmHg after a week of treatment and the IOP remained below 20 mmHg for the duration of the study (Fig. 1).

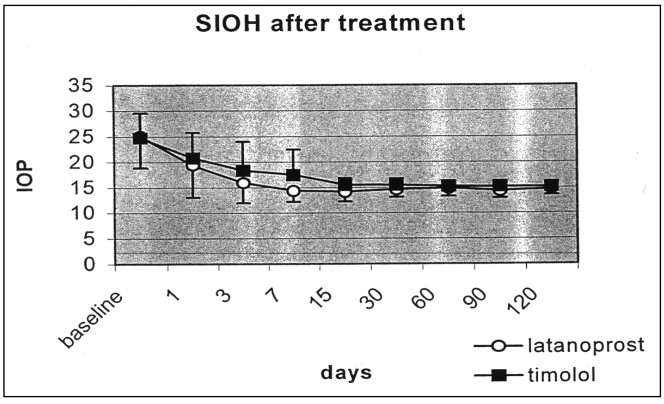

Fig. 1 - *Intraocular pressure (mean ± SD) at baseline and at eight follow-up timepoints in patients given latanoprost or timolol.*

TABLE I - PREOPERATIVE INDEPENDENT VARIABLES

Characteristics	Group A (latanoprost)	Group B (timolol)	p value
Number of patients	15	14	
Sex (M/F)	7/8	7/7	0.847*
Age (yrs) (mean ± SD)	27.47 ± 3.523	28.14 ± 3.592	0.613°
Myopic error (D) (mean ± SD)	5.933 ± 1.657	5.768 ± 1.63	0.789°
Basal IOP (mmHg) (mean ± SD)	14.07 ± 1.328	14.13 ± 1.407	0.904°

* Chi-square test (p<0.05)
° ANOVA (p<0.05)

TABLE II - INTRAOCULAR PRESSURE IN PATIENTS GIVEN LATANOPROST (GROUP A) OR TIMOLOL (GROUP B)

Group A	**Peak**	**Post-peak timepoints (days)**							
	IOP	1	3	7	15	30	60	90	120
Mean (mmHg)	25.07	19.33	15.87	14.33	14.21	14.60	14.80	14.40	14.67
(SD)	(6.17)	(6.37)	(3.94)	(2.19)	(1.89)	(1.55)	(1.57)	(1.45)	(1.18)
No. patients	15	15	15	15	15	15	15	15	15
Group B									
Mean (mmHg)	24.71	20.79	18.36	17.50	15.65	15.43	15.21	15.14	15.14
(SD)	(4.89)	(4.96)	(5.64)	(4.97)	(1.33)	(1.28)	(1.05)	(1.15)	(1.03)
No. patients	14	14	14	14	12*	12*	12*	12*	12*
p	0.864	0.499	0.177	0.033	0.026	0.149	0.446	0.162	0.287

*Two patients did not respond to timolol after seven days and latanoprost was added to the protocol. As the results were not comparable, they were excluded from the analysis

TABLE III – OCULAR SIDE EFFECTS: NUMBERS OF PATIENTS

	Group A	**Group B**	**P value***
Conjunctival hyperemia	2 (13.3%)	1 (7.7%)	0.950
Foreign body sensation	1 (6.6%)	0 (0%)	0.972
Burning	1 (6.6%)	2 (14.2%)	0.950
Itching	0 (0%)	2 (14.2%)	0.433
Stinging	2 (13.3%)	1 (7.7%)	0.950
Tearing	0 (0%)	1 (7.7%)	0.972
Eye pain	1 (6.6%)	1 (7.7%)	0.495
Eyelid inflammation	1 (6.6%)	1 (7.7%)	0.495

* Chi-square test ($p<0.05$)

Five of the 14 patients in group B (35.7%) achieved IOP less than 20 mmHg within 24 hours and 11 (78.5%) achieved this lowering after three days of treatment. In two patients IOP was still higher than 20 mmHg after a week of treatment (24 and 26 mmHg, respectively) and they were excluded from analysis. These two patients, however, achieved IOP less than 20 mmHg as soon as latanoprost was added.

Table III summarizes the ocular side effects. There were no significant differences between groups.

DISCUSSION

SIOH is a well-known complication of post-PRK steroid therapy. Therapeutic management of this kind of ocular hypertension is hard: SIOH calls for sudden resolution, but at the same time steroids are necessary to control regression and haze, especially in highly myopic patients (27, 30).

Even though the effect of steroids on the trabecular meshwork has already been clarified, a definitive etiopathogenic theory has still to be developed and many have been formulated: SIOH may be due to glycosaminoglycan deposits in the trabecular meshwork which occlude or narrow outflow pores, increasing aqueous outflow resistance (1, 2, 12), or to the reduction of prostaglandin production, as suggested by Francois (31, 32), or even to the inhibition of the phagocytosis mechanism of the endothelial cells of the trabecular meshwork (33-35).

Managing a SIOH patient, therefore, poses a multiple therapeutic choice: lowering IOP simply by suspending steroids, either to control aqueous production or to enhance outflow. As stated above, we believe that steroids are important in post-PRK therapy so we did not suspend steroid therapy in our study. Thus, we compared latanoprost (36), which is effective on the aqueous humour outflow, with timolol, acting on the aqueous humour production. Although the conventional outflow pathway was interrupted, latanoprost normalized IOP in all treated eyes.

This definitely confirmed the importance of an alternative outflow pathway through the uveoscleral route (37-41), which is close to the trabecular meshwork, but responds to independent hydrodynamic regulation. Moreover, activation of the uveo-scleral outflow

avoids chronic excessive reduction of aqueous humour formation, which is frequent during timolol treatment. The reduction of aqueous humour can lead to adverse effects on avascular ocular structures, which depend on aqueous flow for metabolic exchange (42).

Even though both drugs were effective in this short-term study (120 days), latanoprost already induced significantly lower IOP than timolol after 7 and 15 days. We also noticed a marked efficacy even in cases where β-blockers failed to reduce aqueous production: in both the cases here, IOP control was obtained only when latanoprost was given in addition to timolol.

Short-term steroid therapy (about three months) did not require prolonged treatments with latanoprost and patients complained of no iris chromatic changes. None of the other well-documented and sight-threatening side effects of latanoprost, such as herpetic keratitis (43, 44), acute anterior uveitis with keratic precipitate (45, 46), choroidal detachments (47), or cystic macular oedema (46-48), were reported. The long half-life of latanoprost, permits once-a-day administration, whereas all other classes of glaucoma drugs, such as β-blockers, require twice-a-day instillations.

Although the drug was well tolerated, some patients in both groups complained of ocular discomfort without any significant difference. A comparison of our results and other similar studies (49-51) is not reliable, considering the size and specific characteristics of our sample. Post-PRK re-epithelialized cornea is particularly reactive and, together with inadequate tear film regeneration, could mimic the symptoms and signs we evaluated. Nevertheless, the incidence of ocular discomfort signs and symptoms was generally lower than in the other studies (49-51). This could be explained by the inhibition of the inflammatory pathway due to steroid therapy (52, 53), if we assume that side effects can be regarded as part of an inflammatory response (49).

In conclusion, latanoprost can be considered effective on SIOH, with certain properties, such as higher compliance and a prompt tonometric response from the first day, especially evident between the first and second weeks of therapy, which make it recommendable in this specific class of ocular hypertension. Even though no sight-threatening complications were reported, further investigations with larger numbers of patients are necessary to prove that latanoprost has no troublesome side effects. Steroid-induced ocular hypertension after PRK could be a good model for highlighting the role of uveo-scleral outflow, which was hitherto believed to be less important than trabecular outflow in ocular hydrodynamics.

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