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Pilot study to evaluate the efficacy and safety of pneumatic trabeculoplasty in glaucoma and ocular hypertension

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PURPOSE. Following laser-assisted in situ keratomileusis (LASIK), intraocular pressure (IOP) is measurably lower in a significant number of cases. It has been proposed that the decrease in IOP may be a real event. Prior trials have evaluated pneumatic trabeculoplasty (PNT) in combination with concomitant glaucoma medications. The aim of this study was to determine the efficacy and the safety of PNT alone to lower IOP in patients with primary open angle glaucoma (POAG) or ocular hypertension (OH).

METHODS AND RESULTS. A total of 37 subjects with POAG or OH were enrolled in a prospective, open-label, fellow-eye, multicenter trial to determine the IOP lowering effects of PNT. All subjects underwent ophthalmologic examinations and IOP measurements and were washed out from all glaucoma medications prior to the start of the study. The trial was intrapatient controlled for the first 30 days, with one eye receiving PNT at days 0 and 7 and the fellow eye serving as the control. The second eye was treated with PNT at day 30. The patients were followed for 120 days, with the first eye receiving an additional PNT treatment at days 90 and 97. Two analyses-an intent to treat analysis in which the last IOP measurement for patients dropped from the study was carried forward and an analysis including only those patients who completed the trial-were performed. Of the 37 patients enrolled, 27 (73%) completed the study. For the intent to treat analysis the baseline mean IOP was 24.7±1.9 mmHg for eye 1 and 23.6±2.3 mmHg for eye 2 and the difference was statistically significant ($p<0.05$). Using this analysis the differences between eye 1 mean IOP at days 1, 7, 14, and 60 and the baseline mean IOP were statistically significant ($p<0.05$). The differences between eye 2 mean IOP and the baseline mean IOP were statistically significant ($p<0.05$) at all time points except day 14 and day 30. The greater mean IOP reductions from the baseline mean IOP for eye 1 were at study day 1 (-16,1%), day 14 (-9%), and day 60 (-8.9%). For eye 2 they were at day 60 (-8.7%) and at day 120 (-9.1%). For the analysis that included only those subjects who completed the trial the decrease in eye 1 mean IOP from baseline was statistically significant ($p<0.05$) at all time points. The decrease in eye 2 mean IOP from baseline was statistically significant at all time points except day 30. Using this analysis the greater mean IOP reductions from the baseline mean IOP for eye 1 were at study day 1 (-19%), day 14 (-15.7%), day 37 (-16.3%), day 60 (-20.0%), day 90 (-18.1%), day 97 (-16.8%), and day 120 (-15.8%). For eye 2 greater mean IOP reductions from baseline mean IOP were seen on day 37 (-13.0%), day 60 (-16.7%), day 90 (-15.5%), day 97 (-14.5%), and day 120 (-17.2%). No statistically significant differences were found in mean IOP reduction between the two eyes treated. A total of 34 patients (92%) showed adverse effects: conjunctival hyperemia in 26 (70.3%) and conjunctival hemorrhage in 14 (37.8%).

CONCLUSIONS. This pilot study of PNT showed a potentially good IOP lowering effect on glaucoma and hypertensive patients. Additional studies would help to better define the types of patients who respond to PNT and to identify risk factors that may lead to treatment failure. (Eur J Ophthalmol 2005; 15:347-52)

KEY WORDS. Ocular hypertension, Primary open angle glaucoma, Pneumatic trabeculoplasty

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INTRODUCTION

Following laser-assisted in situ keratomileusis (LASIK), intraocular pressure (IOP) is measurably lower in a significant number of cases (1-3). There have been many reasons postulated for this observed drop in IOP, the most frequent being that the resultant decrease is an artifact secondary to central corneal thinning associated with a change in corneal rigidity due to the interruption of Bowman's membrane. LiVecchi has previously proposed that the decrease in IOP is a real event and tested this hypothesis on a handful of normal subjects and patients with ocular hypertension (OHT) with promising results (4). Bores et al (4) have presented data on a retrospective analysis of 177 patients, which showed a significant reduction in concomitant medications when pneumatic trabeculoplasty (PNT) was incorporated into the treatment regime. Bores et al (4) also presented data on a retrospective analysis of patients treated in a separate study at a different facility that confirmed the previous findings. Bores et al also reported on a 49-patient study by Fyodorov in which they found that glaucoma patients, who were on multiple medications and/or had prior multiple surgeries, did not respond as well to PNT. Harris et al (5) reported on an eight-patient study in which they did not observe a decrease in IOP in patients who were maintained on their medication following PNT. Unlike the previously referenced studies, no attempt at medication reduction was undertaken. It was postulated by the authors, as well as by Bores et al, that the patient numbers may have been insufficient and/or the starting IOPs too low to allow detection of an IOP change.

The aim of this study was to determine the efficacy and safety of PNT in lowering IOP in patients with primary open angle glaucoma (POAG) or OHT.

MATERIALS AND METHODS

A prospective, multicenter, controlled, open label trial was conducted on 37 POAG or OHT patients (20 male, 17 female) with an IOP > 22 mmHg on monotherapy or without any treatment. The protocol, approved by the university internal ethics committee, was in agreement with the Declaration of Helsinki (1996) and eligible patients were enrolled in the study during the screening visit after signing an informed consent.

Inclusion criteria were 18 years of age or older and a diagnosis of POAG (including pseudoexfoliative or pigmentary glaucoma) or OHT with an IOP > 22 mmHg without any therapy. Patients underwent an adequate washout if they were on glaucoma medication (Tab. I). Exclusion criteria were history of progressive retinal or optic nerve disease other than POAG, age-related macular degeneration, clinically significant corneal disorders, prior filtering surgery or any other kind of ocular surgery, intraocular inflammation within the past 5 years, or uncontrolled systemic diseases.

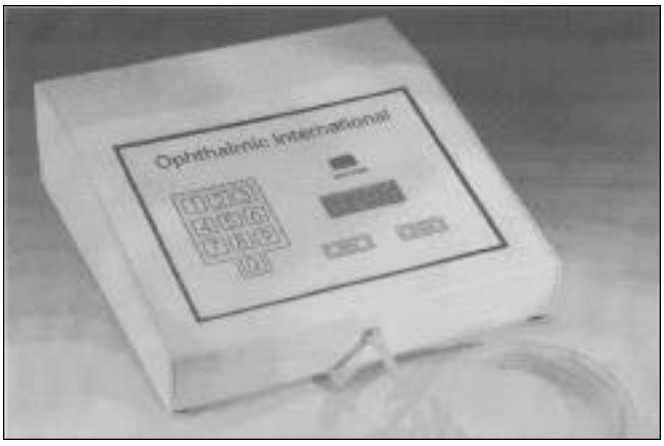

Fig. 1 - Pneumatic trabeculoplasty (PNT) Model 1000 (Ophthalmic International, Inc., Fountain Hills, AZ).

The diagnosis of glaucoma required visual field defects compatible with glaucoma and not explained by other causes and documented by static computerized perimetry with the 24-2 test pattern and SITA standard strategy using a size III white stimulus on a white background. The definition of a glaucomatous visual field defect required at least two reliable tests, performed on different days in the last 1 year, which were classified as outside normal limits by the Glaucoma Hemifield Test (GHT) affecting the same GHT sector. The diagnosis of OHT required an IOP between 22 and 35 mmHg in one eye, measured on at least two occasions, along with being classified as within normal limits by the GHT.

At the screening visit, and all other scheduled visits, the patients underwent visual acuity, biomicroscopy, applanation tonometry, gonioscopy, and ophthalmoscopy. Patients underwent visual field test at the baseline visit and at the end of the study. IOP was measured twice in each eye, between 8:00 and 10:00 am before PNT (Fig. 1) application during each follow-up visit, using Goldmann applanation tonometry, and if the difference between the first and second reading was greater than 2 mmHg a third reading was taken. IOP was reported as either the mean

TABLE I - WASHOUT PERIOD FOR DIFFERENT CLASSES OF ANTIGLAUCOMA MEDICATION

Medication class	Time for washout
Topical beta blockers	3 wk
Topical prostaglandins	3 wk
Topical alpha agonists	2 wk
Topical epinephrine-related products	2 wk
Topical or systemic CAIs	3 d
Topical pilocarpines	3 d

TABLE II - PATIENT DEMOGRAPHIC CHARACTERISTICS

Characteristics	PNT, n=37
Sex, n (%)	
Female	17 (46)
Male	20 (54)
Age, y	
Mean	60.9±10.4
Range	41–82
Diagnosis, n (%)	
OHT	22 (59)
POAG	15 (40.5)
Duration of diagnosis, yr	
Mean	8.1
Range	0.0–22.8

OHT = Ocular hypertension; POAG = Primary open-angle glaucoma

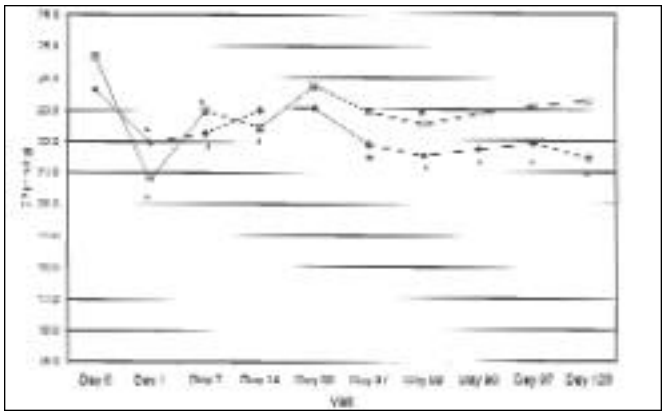

Fig. 2 - Intent-to-treat patients, mean intraocular pressure (IOP) for EYE 1 and EYE 2 at each visit (n=37). ❑ = EYE 1; ■ = EYE 2. Patients withdrawn for uncontrolled IOP had last IOP observation carried forward.
* Indicates change from baseline is significant.

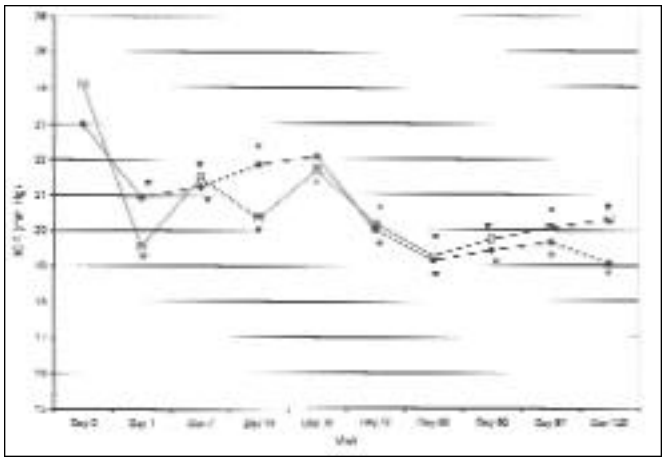

Fig. 3 - Patients completing study, mean intraocular pressure (IOP) for EYE 1 and 2 at each visit (n=27). ❑ = EYE 1; ■ = EYE 2.
* Indicates change from baseline is significant.

TABLE III - IOP MEANS AND SD VALUES AT EACH TIME VISIT FOR INTENT-TO-TREAT ANALYSIS AND ANALYSIS OF SUBJECTS COMPLETING STUDY

	Intent-to-treat analysis			Subjects completing study (n=27)	
Visit	EYE 1	EYE 2	N	EYE 1	EYE 2
Day 0	24.7±1.9	23.6±2.3	37	24.1±1.6	23.1±1.5
Day 1	20.8±4.2	22.0±3.3	37	19.5±2.5	20.9±2.8
Day 7	23.2±4.2	22.2±3.0	36	21.5±3.0	21.2±2.2
Day 14	22.4±5.3	23.0±3.5	36	20.3±2.7	21.9±2.4
Day 30	23.8±5.1	23.1±3.6	32	21.7±2.4	22.1±2.5
Day 37	22.9±6.2	21.9±4.9	31	20.2±3.2	20.0±3.2
Day 60	22.5±6.3	21.5±5.3	29	19.3±2.3	19.1±2.8
Day 90	22.9±6.4	21.7±5.2	27	19.7±3.2	19.4±2.7
Day 97	23.1±6.4	21.9±5.2	27	20.1±3.5	19.7±3.0
Day 120	23.3±6.2	21.5±5.2	27	20.3±3.0	19.0±2.5

Values are mean intraocular pressure (IOP) (mmHg) ± SD

of two readings or the median of three readings. At baseline, after appropriate washout from previous therapy, the eye with the higher morning IOP was chosen to receive PNT treatment. If the IOP was equal in both eyes the left eye was designated to receive treatment. The first eye, EYE 1, received a PNT treatment on day 0 (baseline) and after 7 days (Fig. 2). During the first 30 days the fellow eye was used as an intrasubject control; then it was scheduled to receive PNT treatment on days 30 and 37 (EYE 2). EYE 1 received an additional PNT treatment after 3 months (90 and 97 days).

The PNT procedure was performed with the patient in a supine position. Tetracaine 0.5% ophthalmic solution was administered to the eye selected to undergo the PNT treatment. The lids were gently spread by the physician using his fingers or a wire lid speculum. The presterilized PNT ring was then centered on the clear cornea using a slight downward pressure to facilitate the initial attachment of the ring as a vacuum of 20 inches of Hg was applied to the ring. The duration of vacuum application was 60 seconds. Care was taken, following initiation of the vacuum cycle, not to twist the connection tubing as it could put unnecessary stress on the ring/eye interface. Just prior to the completion of the vacuum cycle a slight downward pressure was applied to the ring in order to prevent a sudden release of the ring from the eye, which might startle the patient. After a rest period of 5 minutes, the PNT procedure was repeated on the eye being treated. One drop of antibiotic was then administered to the treated eye. The combination of a PNT application, a 5-minute rest period, followed by another PNT application constituted a complete PNT treatment. Ocular changes were evaluated after PNT treatment.

Paired and unpaired sample two-tailed t-tests were used to compare continuous normal variables for within-group and between group changes. A $p<0.05$ was considered statistically significant. Two separate analyses were performed: an intent-to-treat analysis, which included all patients enrolled in the study, and an analysis in which only those patients who completed the study were included.

RESULTS

Of the 37 patients enrolled, 27 (73%) completed the study. For the intent-to-treat analysis we have included the patients who withdrew for uncontrolled IOP by carrying forward the last IOP observation. A statistical evaluation, which included only those subjects completing the trial, was also performed. Mean age was 60.9±10.4, range 41–82 years (Tab. II). Nine patients (24.3%) discontinued the study for uncontrolled IOP.

For the intent-to-treat analysis the baseline mean IOP was 24.7±1.9 mmHg for EYE 1 and 23.6±2.3 mmHg for EYE 2 and the difference between mean baseline IOP was statistically significant ($p<0.05$). This analysis of the differences between EYE 1 mean IOP at days 1, 7, 14, and 60 and the baseline mean IOP was statistically significant ($p<0.05$). No statistically significant differences were found at other scheduled follow-up visits (days 30, 37, 90, 97, and 120). The differences between EYE 2 mean IOP at days 1, 7, 37, 60, 90, 97, and 120 and the baseline mean IOP were statistically significant ($p<0.05$). The comparison between EYE 1 mean IOP and the intrasubject control EYE 2 for the first 30 days was not statistically significant at days 1, 7, 14, and 30 (Tab. III).

For the analysis including only those subjects who completed the study the baseline mean IOP was 24.1±1.6 mmHg for EYE 1 and 23.1±1.5 mmHg for EYE 2 and the difference between mean baseline IOP was statistically significant ($p<0.05$). The differences between EYE 1 mean IOP at all time points and the baseline mean IOP were statistically significant ($p<0.05$).

The differences between EYE 2 mean IOP and the baseline mean IOP were statistically significant ($p<0.05$) at all time points except day 30. The comparison between EYE 1 mean IOP and the intrasubject control EYE2 for the first 30 days was statistically significant at days 1 and 14 ($p<0.05$) and not significant at the other follow-up visits (Fig. 3).

Mean IOP and standard deviation values at each time point, for both the intent-to-treat and the analysis including only subjects who completed the trial, are shown in Table III.

The percent change from baseline IOP was also evaluated. For the intent-to-treat analysis the greater mean IOP reduction from the baseline mean IOP for EYE 1 was at study day 1 (-16,1%), day 14 (-9%), and day 60 (-8.9%) and for EYE 2 at day 60 (-8.7%) and at day 120 (-9.1%). No statistically significant differences were found in mean IOP reduction between the two eyes treated, except at day 1 ($p<0.05$).

The evaluation of percent change including those patients who completed the trial showed that the difference between EYE 1 mean IOP at all time points and the base-

line mean IOP was statistically significant ($p<0.05$) and for EYE 2 was statistically significant ($p<0.05$) at every follow-up visit except for day 30 ($p=0.57$). The larger mean IOP reductions from the baseline mean IOP for EYE 1 was at study day 1 (-19%), day 14 (-15.7%), day 37 (-16.3%), day 60 (-20.0%), day 90 (-18.1%), day 97 (-16.8%), and day 120 (-15.8%). For EYE 2 the larger reductions in mean IOP were seen on day 37 (-13.0%), day 60 (-16.7%), day 90 (-15.5%), day 97 (-14.5%), and day 120 (-17.2%).

We also conducted a statistical analysis of the number of patients, at each follow-up visit, having an IOP reduction of at least 15% versus baseline. For EYE 1, 51.3% (19 patients) at day 1, 27% (10 patients) at day 7, 40.5% (15 patients) at day 14, 18.9% (7 patients) at day 30, 37.8% (14 patients) at day 37, 48.6% (18 patients) at day 60, 43.2% (16 patients) at day 90, 45.9% (17 patients) at day 97, and 45.9% (17 patients) at day 120 reached an IOP reduction at least ≥15%. For EYE 2, 18.9% (7 patients) at day 1, 18.9% (7 patients) at day 7, 16.2% (6 patients) at day 14, 21.6% (8 patients) at day 30, 32.4% (12 patients) at day 37, 40.5% (15 patients) at day 60, 48.6% (18 patients) at day 90, 37.8% (14 patients) at day 97, and 45.9% (17 patients) at day 120 reached an IOP reduction at least ≥15%.

No clinically relevant changes were observed in either eye in visual acuity, gonioscopy, ophthalmoscopy, or visual field. However, clinically relevant changes in the slit lamp examinations were noted in the conjunctiva of both eyes following PNT treatments. Thirty-four patients (92%) showed adverse effects. The most common adverse effects were conjunctival hyperemia (26 [70.3%]) and conjunctival hemorrhage (14 [37.8%]). All these events were suspected to be device related. All events resolved without sequelae.

DISCUSSION

In this prospective, multicenter, controlled study performed on 37 POAG and OHT patients, PNT treatment was effective in lowering IOP but the behavior of the IOP reduction is different between the eyes.

PNT is a noninvasive method that has been reported to lower IOP in patients with POAG and OHT. The exact mechanism of the PNT lowering effect has not been elucidated but is believed to act by improving aqueous outflow. Such improvement may occur both at the level of the conventional routes of aqueous outflow, by stretching the trabecular meshwork, and/or by widening the uveoscleral pathways. In the past, perilimbar suction cups were devised for the evaluation of ocular hydrodynamics (6-8). The aim of such techniques was to close the limbar aqueous veins and the collector channels in order to block the aqueous outflow pathways. The wide size of the cup surface and the amount of the depression into the cup were sufficient to close the channels but not to produce a significant scleral indentation and therefore no change of the trabecular meshwork was invoked.

In the case of PNT, a possible stretching of the meshwork may be obtained due to both the shape of the ring and the more consistent vacuum derived with such a device. In our data, PNT has shown a significant IOP lowering effect in the short term in EYE 1. Also, at day 60, EYE 1 shows an IOP reduction that is statistically significant. These data may be correlated to EYE 2 following PNT treatment at day 30 and 37 and may influence EYE 1 IOP.

The IOP response of EYE 2 appears to behave differently than EYE 1 following PNT. In fact, there was a significant short term IOP lowering effect following the initial PNT application to EYE 1, although it returned to baseline within a few days. This was observed despite the fact that we had not performed a PNT application on EYE 2 since it served as the control eye for the first month. In addition, following PNT treatment for EYE 2 at days 30 and 37 the IOP lowering effect on EYE 2 lasted for 3 months. A possible hypothesis for these observations is that the treatment of EYE 1 may make EYE 2 more responsive to PNT treatment. This could be due to the autonomic nervous system, perhaps through an influence on systemic blood pressure, having a significant role in IOP regulation (9).

The requirement, in evaluating the data under the intent-to-treat scenario, of carrying the last IOP forward for the remaining time points complicates interpretation of the data in regards to those subjects who demonstrate a response. If we considered the data from the statistical evaluation of those subjects who completed the trial we found a significant IOP lowering effect at each time point for EYE 1. We also observed a significant IOP reduction at days 1 and 7 for EYE 2 (the intrasubject control for the first 30 days), which appears to correlate to the PNT treatment of EYE 1. Significant differences were also observed in EYE 2 on days 30, 37, and 120 following the PNT treatment of EYE 2 on day 30 and in EYE 1 on days 90 and 97 following the second PNT treatment of EYE 1 on day 90. Largest mean percentage IOP reductions from baseline values, in those patients who completed the trial, were

observed immediately following PNT applications.

In addition, we also considered in the statistical analysis the percentage of patients who reached an IOP reduction of at least ≥15%. We decided to use this cutoff because, as suggested by European Guidelines of Glaucoma, any type of treatment is considered to be effective if it achieves an IOP reduction of at least 15%. Using these criteria PNT treatments are effective in a great percentage of patients since they achieve a good lowering effect in both eyes treated. In fact, for EYE 1 after the first day of treatment, more than 50% of patients presented an IOP reduction at least 15% and in the short term (at day 14) 40% of patients showed the same results. Long term, 43% to 48% of patients showed good results. In EYE 2 the percentage of patients achieving a 15% reduction in IOP, following PNT on study day 30, was 32% to 48%. Importantly, EYE 2 did not show IOP spikes following PNT during the follow-up visits.

While this pilot study confirmed that PNT can be used in the management of POAG and OHT by demonstrating a good lowering effect in a great percentage of patients, we also found that 24% of the patients were nonresponders to this therapy. It would be useful to better define the types of patients who respond to PNT by analyzing separate glaucoma forms or by recognizing risk factors that may lead to treatment failure. While this type of treatment may not be suitable as monotherapy in all patients it should be useful in combination with antiglaucoma eye drops, especially with new categories of drugs such as prostaglandins or prostamides, by improving the uveoscleral outflow.

Adverse events were conjunctival hyperemia or hemorrhage, all of which were mild, required no treatment, and resolved within a few days.

In conclusion, this pilot study of PNT showed a potentially good IOP lowering effect on glaucoma and hypertensive patients. Additional studies would help to better define the types of patients who respond to PNT and to identify risk factors that may lead to treatment failure.

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