ORIGINAL ARTICLE

Pneumatic Trabeculoplasty

A New Method to Treat Primary Open-Angle Glaucoma and Reduce the Number of Concomitant Medications

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ABSTRACT

Pneumatic trabeculoplasty (PNT), when used in combination with antiglaucoma medication, was evaluated in two studies: a feasibility study involving 177 patients, and a separate efficacy study involving 317 eyes. Both studies were nonblinded, single-armed, and nonrandomized; the primary efficacy end point in each study was a decrease in intraocular pressure (IOP) compared with baseline. The first study reported a mean drop in IOP of 6.3 mmHg across the entire group. The second study showed a mean IOP after PNT treatment level at least 1 mmHg less than the pretreatment mean; except at 3, 6, 9, and 12 months, when it was at least 2 mmHg less than the initial mean IOP. The lesser reduction observed in the second study can be explained by the fact that a number of the patients were at least partially controlled by antiglaucoma medications at enrollment, and, as a result, the group had a lower starting IOP than those enrolled in the first study. In both studies, a clear trend to less medication was observed when PNT was added to a patient's treatment regime. The ability of PNT to reduce IOP and medication requirements, along with its relatively benign safety profile, supports the use of PNT as part of a glaucoma patient's treatment regimen.

INTRODUCTION

Glaucoma is the second leading cause of irreversible blindness in the United States and the leading cause among African Americans *(1,2)*; 13% of the blindness in the United States is caused by glaucoma, and glaucoma accounts for 12% of new cases of blindness each year *(3)*. Of the various forms of glaucoma (e.g., congenital, open-angle, closed-angle, secondary), primary open-angle glaucoma (POAG) is the most common in the United States (80–90% of cases), and is estimated to be responsible for impaired vision in 1.6 million Americans and blindness in 150,000 Americans *(4,5)*. Annual office visits for glaucoma in the United States increased from roughly 2 million in 1975 to almost 9 million in 1992 *(6)*. POAG is usually asymptomatic until irreversible visual field loss has occurred. One

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Drs. Leo D. Bores and John T. LiVecchi have stated that they do have significant financial interest or other relationship with a product manufacturer or provider of services discussed in this article (Dr. Bores is the Medical Director for Ophthalmic International and Dr. LiVecchi is Medical Director and a member of the Board of Directors of Coronado Industries). Dr. Guillermo Avalos Urzúa has no financial interest the device. The authors also do discuss the use of off-label products, which includes unlabeled, unapproved, or investigative devices.

Submitted for publication: (6/29/04). **Accepted:** (10/6/04).

study reported that over the course of 20 years, blindness may develop in up to 75% of persons with glaucoma *(7)*. There are few data, however, on the natural history of disease in persons with mild visual field defects detected by screening. The incidence of POAG generally increases with age. Leske, in a review of data from various sources, estimated that the incidence was less than 1 in 100 for persons younger than age 65 years, approx 1 in 100 for persons aged 70 years, and approx 3 in 100 for persons older than age 75 years *(2)*. Incidence of glaucoma is increased in patients with diabetes mellitus, myopia, and a family history of glaucoma *(5)*. Additionally, a much larger number of persons have ocular hypertension (usually defined as an intraocular pressure [IOP] ≥21 mmHg), which is a strong risk factor for developing glaucoma. Ocular hypertension is present in 7–13% of the general population, and the prevalence increases with age *(5)*. In the Framingham Study, one-fourth of men and women over age 65 years had ocular hypertension *(8,9)*.

POAG treatment has focused on lowering IOP either by increasing outflow of aqueous humor from the anterior chamber or by reducing production of aqueous humor by the ciliary body. Antiglaucoma medication, topically applied, is traditionally the first attempted therapy, followed by systemic carbonic anhydrase inhibitors, and finally, surgical intervention (if necessary) to control IOP.

Some physicians consider 15 mmHg to be a "magic number" because patients whose IOP is at 15 mmHg or lower statistically show less progression of visual field defects. Generally, progression of visual field loss is reduced if IOP is maintained at or below 15 mmHg. The risk of progressing to glaucoma varies directly with the level of IOP and the duration of follow-up: the proportion of persons developing visual deficits within 5 years was less than 1% for normal IOP less than 21 mmHg, 3–10% for IOP greater than or equal to 21 mmHg, 6–16% for IOP greater than 25 mmHg, and 33% for IOP greater than 30 mmHg *(10)*. Untreated individuals with moderate ocular hypertension (mean IOP 24–26 mmHg) developed new visual deficits (based on sensitive measures) at a rate of 3–4% per year in recent trials *(11–13)*. Among patients with untreated ocular hypertension who were followed for 17–20 years in an older series, over 30% developed clinical glaucoma *(14,15)*.

Poor compliance, variable response to treatment, and a relatively high frequency of side effects make treatment with medications far from ideal. Spooner et al. *(16)* have reported that approx 62% of patients discontinue their initial glaucoma medications and 18% change to a different medication within the first 18 months. Additionally, noncompliance with prescribed dosage regimes is a well-known problem. Many ophthalmologists have patients who present with acceptable IOP levels at follow-up yet show continued deterioration in their visual fields. On careful inquiry, it has been noted that subjects are diligent in taking their medication for the few days before their follow-up visit but are not compliant between check-ups. Ophthalmologists have long been searching for treatment approaches that are as effective as pharmaceuticals when properly administered but with better safety and compliance profiles and fewer risks than the usual forms of surgery.

After refractive procedures, including microlamellar kerato plasty and LASIK, the IOP is measurably lower in a significant number of cases. Many reasons have been postulated for this observed drop in IOP; the most frequent is that the resultant decrease is an artifact secondary to central corneal thinning associated with a change in corneal rigidity resulting from the interruption of Bowman's Membrane. LiVecchi, however, proposed that the decrease in IOP may be a real event (personal communication of author).

Results from two studies evaluating pneumatic trabeculoplasty (PNT) are reported in this manuscript: a feasibility study involving 177 patients performed at an ophthalmology clinic in Guadalajara, Mexico, by Drs. Guillermo Avalos Urzúa and John LiVecchi (the Avalos study) and a 317-eye efficacy study conducted at the Arizona Glaucoma Institute by Dr. Leo D. Bores, (the Bores study). The effectiveness of PNT when used in combination with antiglaucoma medication is evaluated in this manuscript.

MATERIALS AND METHODS

Study Design

Both studies were nonblinded, single-armed, and nonrandomized. The primary efficacy end point in both studies was the decrease in IOP compared with baseline. The IOP measurements were taken with a calibrated Goldmann Applanation Tonometer, the measurements were not blinded, and the time of day was not standardized.

Avalos and LiVecchi performed a preliminary analysis of the medication reduction data obtained in their trial. The medication data from the Bores study was evaluated using a more detailed *post hoc* responder analysis to determine the additional clinical relevance of the medication reduction and its impact on controlling IOP after administration of PNT.

With respect to safety, adverse events were monitored and comprehensive visual examinations were performed

after the procedure to capture any deterioration in visual function compared with baseline in both trials. Although no serious adverse events were anticipated, typical adverse events that may be associated with the PNT procedure include slight postprocedure discomfort, minor inflammation, corneal abrasion, eyelid edema, subconjunctival hemorrhage, subconjunctival edema, and transient blurred vision. Additional rare complications, which could theoretically be associated with the procedure but were not expected to occur, include endothelial cell loss, arterial/venous blockage, and blindness/loss of eye.

Patient Selection

Patient enrollment in both trials allowed males and females of any age or ethnic background with either previously diagnosed POAG or ocular hypertension. Some patients with glaucoma caused by pigmentary dispersion or pseudoexfoliation of the lens capsule were also enrolled. In the Avalos study, two patients with glaucoma associated with traumatic angle recession were also treated.

Prior trabeculectomies, penetrating keratoplasties, corneal transplants, diabetes with rubeosis iridis, severe cupping/narrow angles, and/or extensive visual field changes (i.e., only a central island of vision) were considered criteria for exclusion in these investigations.

General Description of the PNT Procedure

The PNT procedure is best performed with the patient in a supine position. A Chan wrist-rest or similar device to support the physician's hands may also be useful. After the administration of a suitable topical anesthetic, the lids are gently spread with the physician's fingers or with a Barraquer wire lid speculum. The PNT ring (Fig. 1) is centered on the clear cornea using a slight downward pressure to facilitate initial attachment when the vacuum is first applied to the ring. In the case of narrowed palpebral fissures, it is helpful for the patient to look up, whereupon the ring is moved down into the inferior cul-de-sac until the upper lid is cleared.

Good suction can be aided by insuring that the eye is wet when the ring is first applied. Excess downward pressure of the ring by the physician should be avoided because excess pressure may result in the eye being pressed backwards into the socket, causing discomfort to the patient when the smooth edge of the ring contacts the bony orbit. Once the vacuum has been initiated, care should be taken not to twist the connection tubing as it may put unnecessary stress on the ring/eye interface. To this end, passing the suction tubing through the ring of an iv stand or similar support may be helpful.

The duration of vacuum application is 60 seconds. Just before the completion of the vacuum cycle, a slight downward pressure on the ring will prevent the PNT

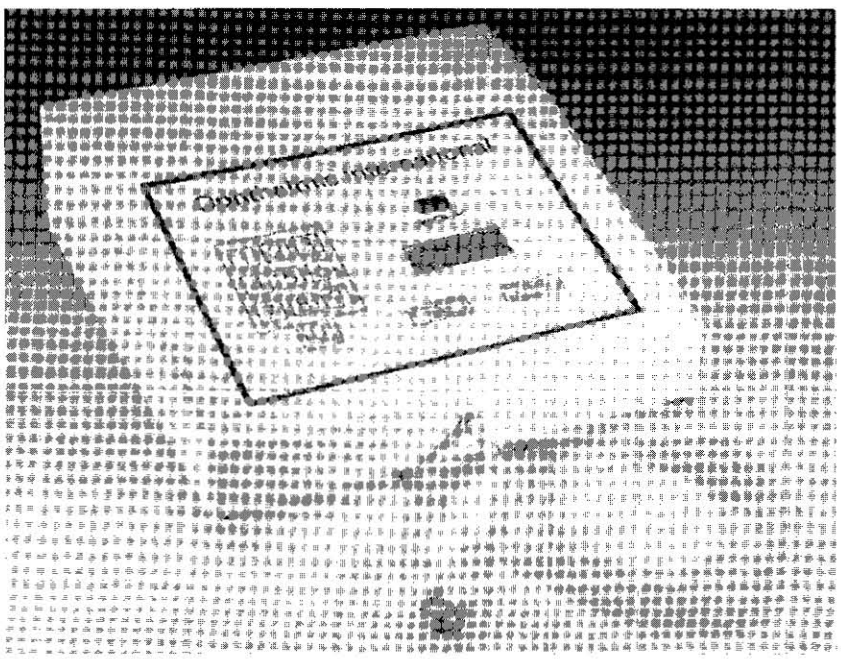

Figure 1—Photograph of pneumatic trabeculoplasty (PNT) equipment including the PNT ring.

ring from suddenly releasing from the eye when the vacuum is terminated. A sudden release of the ring may startle the patient and result in some discomfort.

A PNT application is then usually performed on the other eye. After a rest period of 5 minutes, another PNT application is repeated on each eye. This combination of a PNT application and a 5-minute rest period followed by another PNT application constitutes a single PNT treatment.

Patient Follow-Up

Investigators were required to use patient work-up sheets to document the results at each visit. The information on the patient work-up sheet was entered into a database for later analysis. Investigators who experienced a problem were instructed to contact the sponsor, monitor, or Institutional Review Board. Informed consent was obtained from all patients, and Institutional Review Board approval was provided. Comprehensive visual examinations, including visual acuity, refraction, IOP measurements, slit lamp and fundus examinations, goniscopy, and automated visual fields were performed at visits 1, 6, and 7. An abbreviated visual examination including visual acuity, slit lamp, and IOP measurements were performed at all other visits.

- Visit 1 (baseline exam): obtain medical and ocular history. Comprehensive visual examination on both eyes. Obtain informed consent if eligible for PNT.
- Visit 2 (treatment): PNT treatment, abbreviated visual examination before treatment.
- Visit 3 (1-week follow-up): abbreviated visual examination, perform PNT.
- Visit 4 (2-week follow-up): abbreviated visual examination.
- Visit 5 (1-month follow-up): abbreviated visual examination.
- Visit 6 (3-month follow-up): comprehensive visual examination for both eyes. PNT treatment as necessary.
- Visit 7 (6-month follow-up): comprehensive visual examination for both eyes. PNT treatment as necessary.

Concomitant medical treatments were normally continued for the first 30 days after initiation of PNT. A program to reduce the number and dosage of concomitant medications was then initiated until a stable IOP was achieved. At the 3-month follow-up, IOP was re-evaluated in all cases, and, if significantly elevated, the PNT procedure was repeated. Patients were allowed to continue with PNT treatments, if warranted, at the end of the 6-month period.

Statistical Methods

Both studies were nonblinded, single-armed, and nonrandomized. The primary efficacy end point in both studies was the decrease in IOP compared with baseline. The IOP data was evaluated by assessing changes in the mean IOP before and after PNT and by trends in the range of the data. A more detailed analysis of the IOP data was not feasible because in parallel to the introduction of PNT there was a reduction in concomitant antiglaucoma medication.

The medication reduction data was evaluated as follows:

1. In the Avalos study, the medication reduction data was evaluated by evaluating trends in the absolute number of medications required to control a patient's IOP after the introduction of PNT into their treatment regime.
2. In the Bores study, the medication reduction data was evaluated by employing a more detailed responder analysis, using the following clinically relevant definitions:
   a. An elevated pre-PNT IOP was greater than or equal to 21 mmHg.
   b. A controlled post-PNT IOP was less than or equal to 18 mmHg.
   c. A significant reduction in IOP was a drop of greater than or equal to 5 mmHg.

The benefit of using a responder analysis when multiple parameters are altered in parallel is that a study subject can be clearly categorized as either a responder or nonresponder based on the clinical criteria employed. By carefully defining clinically relevant response criteria, clear, clinically relevant, trends in the overall response of patient groups can be readily elucidated.

RESULTS

The Avalos feasibility study began in late 1994, with Avalos and LiVecchi collecting data on 177 glaucoma patients who had PNT incorporated into their treatment algorithms. A PNT treatment was performed at the first treatment visit (visit 2), was repeated 1 week later, and then as needed, on average at 3–4 month intervals thereafter. The patient population ranged in age from 33 to 82 years and was 56% female. At enrollment, the patient's IOP needed to be above 18 mmHg. The mean follow-up was 48 months, with the shortest follow-up being 24 months and longest the follow-up being 84 months.

The Bores study was initiated at the Arizona Glaucoma Institute in August of 1997. It included 317 eyes of 172 patients with the longest follow-up being 18 months. All patients were maintained on their original antiglaucoma medication(s) during the first PNT cycle, and their medication(s) were subsequently adjusted

appropriately. There were more females than males enrolled in the study. The mean age for males was 67 ± 13.7 years, with a range of 26–85 years; and 71 ± 14.3 years for females, with a range of 28 to 91 years. The Bores study enrolled both patients with IOP above 18 mmHg while on their antiglaucoma medications and patients with IOP less than or equal to 18 mmHg who were on multiple medications and might benefit by experiencing a medication reduction after the addition of PNT to their treatment regime. A majority of the patients treated had a diagnosis with open-angle glaucoma, although some patients with pigmentary glaucoma, pseudoexfoliation, or ocular hypertension were also enrolled.

Efficacy Parameters

IOP Reduction

Relevant study parameters, including IOP before and after PNT from the Avalos study, are summarized in Table 1. It should be noted that subjects enrolled in the Avalos study had, on average, a higher pretreatment IOP than those enrolled in the Bores study. A mean drop in IOP of 6.3 mmHg across the entire group was observed the Avalos study. There was also a significant reduction in the IOP range observed in the patient population.

In the Bores study, the mean IOP after PNT treatment was consistently at least 1 mmHg less than the pretreatment mean in the Avalos study, except at 3, 6, 9, and 12 months, when it was at least 2 mmHg less than the initial mean IOP.

There were clear positive trends in the IOP data after PNT. Before initiation of PNT, 69.4% (220 of 317) of the eyes had IOP controlled (at ≤18 mmHg) with medication alone. A total of 79.3% (184 of 232) of the eyes measured at 1 month after PNT had IOP controlled at less than or equal to 18 mmHg, many of which also had a reduction in their antiglaucoma medication. The improvement was maintained throughout the study, with IOP controlled in 77.8% (119 of 153) of eyes at 3 months, in 81.4% (83 of 102) of eyes at 6 months, and in 79.7% (55 of 69) of eyes at 9 months.

The scatter in the IOP among the group seemed to be reduced after PNT. For example, the pretreatment range of IOP was 8–48 mmHg, and at 9 months the range was 8–29 mmHg in the same group.

TABLE 1

Summary of Relevant Patient and Study Parameters From the Avalos Feasibility Study

Patients	177
Mean age	65.3 years
Mean follow-up	23.5 months
Pretreatment IOP range (mmHg)	19–36
Post-treatment IOP range (mmHg)	13–32
Mean pretreatment IOP (mmHg)	23.4
Mean posttreatment IOP (mmHg)	17.1
Mean IOP drop (mmHg)	6.3

IOP, intraocular pressure.

Concomitant Medication Use

Avalos/Li Vecchi Study

A clear trend toward less medication usage across the group was observed in the study. At enrollment, eight patients were on no medications of any kind before the PNT treatment. Of the remainder, 33 patients were on one medication (a β-blocker); 68 patients were on two medications (a β-blocker and pilocarpine); 24 patients were on three medications (β-blockers, pilocarpine, and an adrenergic); and 44 patients were on four medications (a β-blocker, pilocarpine, adrenergic, and an oral carbonic anhydrase inhibitor). Forty-seven eyes had previously undergone argon laser trabeculoplasty. Of the entire group, 19 eyes went on to require filtering procedures, 5 of these with capsular exfoliation and 1 with recessed angle due to trauma. The remaining recessed angle achieved a reduction of IOP to less than 14 mmHg (from 23). With PNT incorporated as part of a patient's treatment regime, a clear shift to less concomitant medication(s) to control the patient's IOP was observed, Table 2. At the 24 months time point, 65 patients required no additional medication, 34 patients remained on 1 medication; 33 on 2; 14 on 3; and 31 on 4 medications.

Of the 47 patients who were treated with PNT for 84 months, 6 patients (12.7%) remained off all medications. At total of 17 patients (36%) were on PNT and one medication, and 11 patients (23.1%) remained on PNT with two medications to control their IOP. Thirteen patients (24%) remained on their original medications schedule along with PNT and had IOP lower than their original baseline on medication alone. No progression in visual field (VF) has been seen in this group to date.

TABLE 2

Concomitant Medication Usage Before and After Inclusion of Pneumatic Trabeculoplasty (PNT) in Patient's Treatment Regime From the Avalos/Li Vecchi Study

Medications	Initial	After PNT (at mean follow-up)[a]
No medications	8	65
One medication (β-blocker alone)	33	34
Two medications (β-blocker + pilocarpine)	68	33
Three medications (β-blocker + pilocarpine + adrenergic)	24	14
Four medications (β-blocker + pilocarpine + adrenergic + diamox)	44	31

[a]Nineteen eyes went on to require filtering procedures: five eyes with capsular exfoliation and one eye with recessed angle caused by trauma.

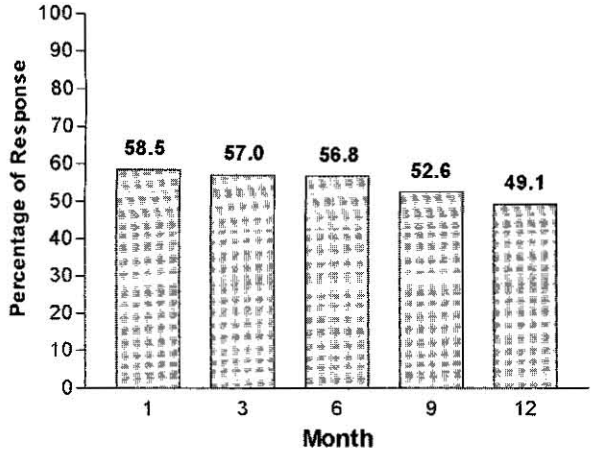

Figure 2—Summary of responder rates for eyes on antiglaucoma medications at baseline which respond after pneumatic trabeculoplasty with an intraocular pressure less than or equal to 18 mmHg *and* a reduction in concomitant medication requirements.

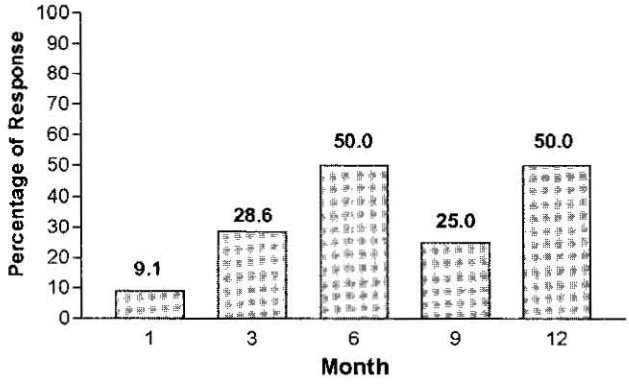

Figure 3—Summary of responder rates for eyes with an elevated intraocular pressure (IOP) greater than or equal to 21 mmHg without antiglaucoma medication responded following pneumatic trabeculoplasty with an IOP of less than or equal to 18 mmHg.

Bores Study

A responder analysis was performed to determine the clinical relevance of the medication reduction in the Bores study. As stated previously, 317 eyes from 172 patients were involved in this study. However, during the study, not all of the eyes were assessed at all times: baseline (week 0), 1, 3, 6, 9, and 12 months. For the purposes of the responder analysis, the data for an eye was included if the number of medications at enrollment (beginning medication requirement), the number of medications at the final IOP measurement (ending medication requirement), the IOP at week 0 (starting IOP), and an IOP at any of months 1, 3, 6, 9, or 12 were available. The data on 247 eyes (77.9%) from 132 patients satisfied these requirements.

Figures 2–5 summarize the responder analysis. The denominator used in calculating the percentage of patients showing a positive response at any time point was the total number of eyes satisfying the clinical response criteria at that specific time point. The figures give the percentage of eyes having a positive response for each of the proposed response criteria.

Eyes in the first group (Fig. 2) included all eyes that were on antiglaucoma medication(s) before enrollment in the study, whether their IOP was elevated (IOP ≥ 21 mmHg) or controlled (IOP ≤ 18 mmHg). This group encompassed the majority of eyes in the analysis (195 of 247 eyes). A positive responder was an eye whose post-PNT IOP was under control at less than or equal to 18 mmHg and that also demonstrated a reduction in concomitant medication usage. Simply stated, positive responders were controlled and on less medication. At each assessment point, 50% or more of these eyes

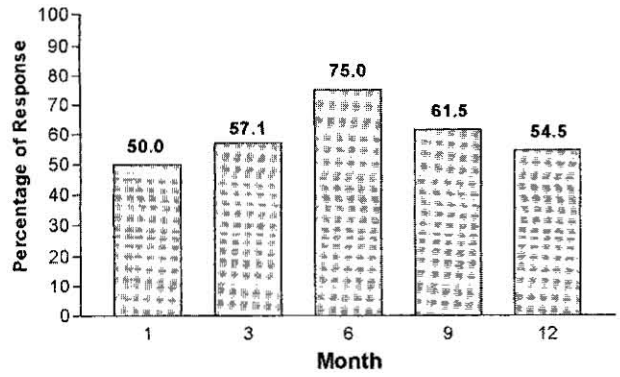

Figure 4—Summary of responder rates for eyes with an elevated intraocular pressure (IOP) of greater than or equal to 21 mmHg while on concomitant medication at baseline and who respond with a IOP after pneumatic trabeculoplasty of less than or equal to 18 mmHg, with or without a reduction in concomitant medication.

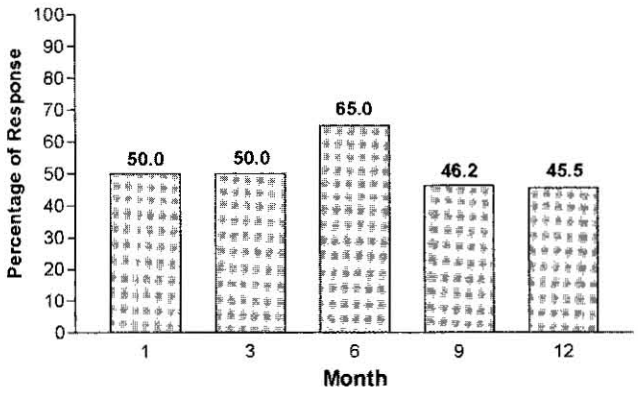

Figure 5—Summary of responder rates for eyes with an elevated intraocular pressure (IOP) greater than or equal to 21 mmHg while on prior therapy at baseline that respond with a significant IOP reduction of greater than or equal to 5 mmHg after pneumatic trabeculoplasty *and* a reduction in concomitant medication.

were deemed positive responders, with IOP under control on less medication.

Eleven eyes had an elevated IOP (≥21 mmHg) and were on no medication (Fig. 3). This group was mutually exclusive of the group of eyes included in Fig. 2. Although the number of eyes falling into this group was small, these eyes most closely represented the newly diagnosed glaucoma patient. A positive responder was defined as an eye with a post-PNT IOP less than or equal to 18 mmHg, which would be considered clinically under control. The responder analysis (Fig. 3) clearly supported that PNT treatments alone were capable of reducing IOP levels to less than or equal to 18 mmHg for some patients.

Thirty-two eyes had been on antiglaucoma medication before enrollment and had an elevated IOP greater than or equal to 21 mmHg. Simply stated, these eyes were clinically uncontrolled on their prior treatment regime. This group represents a subset of eyes also included in Fig. 2. Two different response criteria were examined for this group. In one analysis (Fig. 4), a responder was defined as an eye clinically under control (IOP ≤18 mmHg) after PNT regardless of whether or not they experienced a reduction in medication. Using this criterion, the response rates were consistently over 50% at each time point.

We also examined the same group of 32 eyes employing a positive response criteria of a both a significant reduction in post-PNT IOP (≥5 mmHg) and a reduction in concomitant medication. The response rate ranged from 45.5 to 65.0% over 12 months (Fig. 5), demonstrating that PNT has the ability to significantly reduce IOP even when there is a parallel decrease in antiglaucoma medication.

Safety

The results of each study demonstrated that the side effects of the PNT procedure were generally minor, including mild conjunctival edema and injection, subconjunctival hemorrhage, and mild discomfort. The side effects observed would be expected in any procedure that involves contact with the eye and/or topical analgesia. There were no serious sight-threatening adverse events or complications, and no VF deterioration or retinal nerve damage was observed. In the Bores study, all study subjects had VF analysis using an automated visual field analyzer (VFA; Humphrey Field Analyzer, STATPAC 2/30-2, Carl Zeiss Meditec, Dublin, CA). All patients underwent pretreatment VF on the same machine using the same software setup.

A number of patients received repeat PNT treatments at 3–4 month intervals as an alternative to increasing medication dosages. None of these patients were found to manifest adverse effects or increased rates of visual field changes. Relevant study parameters, including and pre- and post-PNT IOP are summarized in Table 1 for the Avalos study.

DISCUSSION

Efficacy

The difficulty in assessing the IOP results alone for either study was that no patient was excluded from having PNT except for those with previous filtering surgery (in one case there was a trabeculectomy failure, where application of the ring opened the fistula, thereby dropping the IOP to 8 mmHg, where it has remained with a

small bleb; that patient's data were excluded from this analysis). The patients did not undergo a wash-out period before their first PNT treatment. For many patients, IOP was already at least partially controlled with medication; for some patients, the IOP was below 18 mmHg, although requiring multiple antiglaucoma medications. During both studies, the patient's medications were adjusted downward as long as the patient's IOP was maintained within a clinically safe range; thus, PNT was, in effect, working against an increasing IOP baseline. Therefore, the pre- and post-PNT IOP alone does not give a full picture of the potential of PNT in managing the glaucoma patient.

There is no evidence that PNT can induce hypotony in an otherwise normal eye, regardless of whether or not they are on antiglaucoma medication. Because a majority of the study subjects were on antiglaucoma medications at enrollment, their IOP was at least partially controlled. Consequently, the potential for additional IOP decrease with the addition of PNT to a subject's treatment regime was probably muted. This would also explain why the mean drop observed in the Avalos study, in which the eyes on average had a higher mean IOP at enrollment vs the Bores group, was greater than that observed by Bores.

Because a majority of patients were on antiglaucoma medication before PNT, their starting IOP were most likely lower than if they had been washed out before study initiation. The use of IOP changes alone in a trial involving patients on antiglaucoma medications before initiation of a study without a wash-out period is not adequate in evaluating the efficacy of PNT.

Although absolute changes in IOP within this study are difficult to interpret because of the study design, a general trend downward in IOP was observed after PNT. Examination of specific subsets of patients clearly demonstrates that PNT can lower IOP. For example, the examination of the data from Fig. 2, where no medication was used, shows some patients exhibiting a drop in IOP after PNT, which can only be attributed to PNT alone.

In the Bores study, a greater percentage of eyes (approx 10 percentage points) at any time point following PNT administration were found to have IOPs less than or equal to 18 mmHg (i.e., "in control") vs the percentage that had IOPs less than or equal to 18 mmHg at study initiation. This was true even though concomitant medications were being reduced in a number of patients. Long-term improvement in the control of a patient's IOP should translate to better patient outcomes.

Patients on antiglaucoma medications, especially those on multiple medications, often experience troubling side effects. Additionally, compliance decreases, regardless of dosage form, as the number of medications and their frequency of administration increases. Analysis of the data collected during the study clearly supports the ability of PNT to reduce the need for concomitant medication requirements to control a patient's IOP. Approximately 50% of patients who were on medication before PNT (Fig. 2) could be controlled (IOP $\leq$ 18 mmHg) with less medication when PNT was added to their treatment regime. For those who were not controlled on medication alone (Fig. 5), more than 50% of the patients demonstrated at least a 5 mmHg reduction in their IOP after PNT, along with a reduction in concomitant medication. PNT, given its long duration of action and its ability to reduce concomitant medication usage has the potential to improve compliance in the glaucoma population.

The results of these studies differ from a previous published report of eight patients treated with PNT, the Duke study *(17)*. Harris and Allingham concluded from their small cohort that PNT resulted in no significant changes in the IOP after treatment. There were major differences between the Duke study and the ones discussed in this paper. Chief among them is that the patients in the study reported by Harris and Allingham did not complete the prescribed protocol. Additionally, the IOP of patients enrolled in the Duke study were, for the most part, in a normal IOP range of 16–18 mmHg on their medication alone, and medication was not reduced to determine whether the procedure contributed to a reduction in the IOP.

Safety

Regarding safety, no significant adverse events were observed in either study. The adverse events observed were those to be expected when a solid plastic ring is placed in contact with the eye and a vacuum applied, and adverse events associated with using topical anesthesia.

The risks related to the short-term elevation of IOP to levels beyond that considered normal (15–21 mmHg) during application of a vacuum fixation device to the human eye have been carefully reviewed in the literature. The literature is replete with case reports of both central ocular artery and central ocular vein occlusions and their subsequent deleterious effect on both ocular health and vision when such occlusion is prolonged. The application of an external pressure in excess of 45 mmHg can produce occlusion of both the central artery and vein. Ophthalmodynamometry depends on this phenomenon.

The application of a vacuum fixation ring in performing classical keratomileusis or LASIK, in which the

measured IOP can exceed 65 mmHg and in which the elevated pressure may be sustained for upwards of 4–5 minutes, has resulted in only one adverse case being reported. In this circumstance, a case of macular edema, with loss of best corrected visual acuity (BCVA), occurred after a ring application in excess of 8 minutes during a LASIK procedure. This is the only such incident of which the current authors are aware. Major ophthalmic surgery reference texts such as that of Barraquer *(18)* and Bores *(19)* do not consider the use of vacuum fixation rings a risk, nor are eyes with glaucoma necessarily excluded from myopic keratomileusis/LASIK procedures on the basis of a diagnosis of glaucoma. Both the vacuum fixation ring and the keratome have passed US Food and Drug Administration scrutiny in terms of safety and efficacy.

Perusal of the medical literature (National Library of Medicine) as far back as 1963 has resulted in only one article which discusses the actual measurement of IOP during microkeratome sectioning. In the article, Sachs *(20)* broached only the possibility of damage caused by the application of elevated IOP in "eyes at risk"; however, he did not clearly define what was meant by "eyes at risk". In the Sachs study, using pig eyes, the measured IOP exceeded 300 mmHg during corneal sectioning with the microkeratome but only reached 75 mmHg during application of the suction ring alone. The results from this study suggests that if the same degree of IOP elevation results during use of these rings on human eyes, then the human eye is remarkably resistant to short-term elevations of IOP and concomitant short-term occlusion of its circulation.

Macular hemorrhages are a cause of sudden loss of BCVA in high myopes under normal conditions. In an article published in 1996, Kim *(21)* describes a post-LASIK macular hemorrhage in a high myope (≥10 diopters) resulting in two lines of loss of BCVA. He nevertheless describes LASIK surgery as safe and effective, and indicates that this hemorrhage occurred sometime after the LASIK procedure and not as an immediate consequence of the use of a vacuum fixation ring or the microkeratome procedure. However, it seems logical that patients with concurrent wet macular degeneration could be at greater risk.

Although Kim's evaluation above considers risks to the health and condition of the posterior pole of the eye, instances of pre-existing anterior segment disease might also threaten the health of the eye. Any patient who has undergone a recent penetrating keratoplasty (corneal transplant) would be at risk, and hence barred from being treated with PNT. On the other hand, isolated through-and-through and well-healed corneal lacerations would not be necessarily be at risk. Two such eyes have undergone application of PNT without untoward effect.

A diabetic with *rubeosis iridis*, however, often has associated hyphema and/or hemorrhagic glaucoma. Given the fragile nature of the blood vessels in the iris of such eyes, such patients would be barred from having this procedure on theoretical grounds.

Subconjunctival hemorrhages are a frequent finding after application of the vacuum fixation ring. In all of the years of its use for ocular surgery, no such hemorrhage has ever resulted in a major or permanent disability. Aside from a theoretical possibility, clinical experience and the extant literature does not support an increased incidence of ocular infection after benign subconjunctival hemorrhaging. Because the ring is sterile before being placed on the eye, the likelihood of infection from this cause is remote.

Several cases of retinal detachments have been reported after use of the vacuum fixation ring in the LASIK procedure *(22,23)*. No such cases have been reported after classical keratomileusis, however. This may be because the IOP elevation is much higher with the newer microkeratome instruments used for LASIK, particularly during corneal sectioning *(20)*. There may also be a relationship with duration of application of the vacuum, which can exceed 3 minutes during LASIK. The PNT procedure subjects the eye to sustained IOP for only 1 minute and no sectioning of the cornea with its concomitant further increase in IOP in excess of the initial fixation pressure is involved.

The cases reported here of retinal detachment (RD) all occurred in instances of high myopia, which are already at increased risk of RD in any event. The majority of patients who are candidates for PNT are not high myopes. Some, however, have had previous cataract surgery with intraocular lens implantation. The incidence of RD is approx 4% higher in eyes after cataract surgery than in the normal population *(24)*. Keratophakia, the precursor to keratomileusis, was originally employed to correct aphakia (the condition existing after cataract surgery in which no intraocular lens has been implanted) and was not associated with reports of an increased incidence of RD. We are therefore justified in concluding that the risk of RD as a result of PNT is very low.

Some of the patients from the Avalos study have continued to be treated with PNT for up to 7 years with no adverse effects supporting the long-term efficacy and safety of PNT and its ability to control IOP in patients with elevated IOP (glaucoma and ocular hypertensive patients) when incorporated as part of a patient's treatment regime.

SUMMARY

The use of IOP alone in trials involving patients on antiglaucoma medications before initiation of a study that does not include a wash-out period, is not adequate to evaluate the efficacy of PNT. Patients on multiple medications may or may not present with elevated IOP. Therefore, it is important to also determine how well the patient's IOP is controlled and what reduction, if any, in medication requirements might occur.

The results of these studies clearly demonstrate that with the addition of PNT the number of medications can be either reduced or eliminated while still controlling IOP within a satisfactory range. Additionally, for patients on multiple medications whose IOP is not adequately controlled (IOP $\geq$ 21 mmHg), the addition of PNT can significantly reduce the IOP by at least 5 mmHg and, in some cases, bring the IOP back into control ($\leq$18 mmHg) along with a reduction in concomitant medication requirements.

As shown in the Bores study, the percentage of patients with an IOP less than or equal to 18 mmHg after PNT improved by approx 10% vs the percentage of patients meeting this condition at the start of the study. Better control of IOP in a larger percentage of patients should translate to better long-term clinical outcomes. In the Avalos study, a significant number of the subjects (who were under a long-term regime of PNT and antiglaucoma medication) had IOP that were lower than those attained with medication alone. A number of patients were able to reduce or eliminate their medication requirements and maintain their IOP within the safe range for up to 84 months.

As these studies show, the ability of PNT to reduce IOP and medication requirements, along with its relatively benign safety profile, supports the use of PNT as part of a glaucoma patient's treatment regiment. The risks seem to be similar to those associated with other noninvasive ophthalmic tests, such as tonometry or cycloplegia, which may also result in transient elevations in IOP. There is ample data in the extant literature to demonstrate that any theoretical concerns regarding temporary increases in IOP do not present a significant problem in clinical practice *(25)*.

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